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DOCTOR OF PHILOSOPHY

In the Faculty of Humanities



**Associations between Sleep Architecture, Cortisol Concentrations,
Cognitive Performance, and Quality of Life in Patients with Addison's
Disease**

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- a. Henry, M., Thomas, K. G. F., & Ross, I. L. (2014). Episodic memory impairment in Addison's disease: results from a telephonic cognitive assessment. *Metabolic Brain Disease*, 29 (2), 421-430. doi: 10.1007/s11011-014-9511-x
- b. Henry, M., Wolf, P. S. A., Ross, I. L., & Thomas, K. G. F. (2015). Poor quality of life, depressed mood, and memory impairment may be mediated by sleep disruption in patients with Addison's disease. *Physiology and Behavior*, 151, 379-385. doi: 10.1016/j.physbeh.2015.08.011
- c. Henry, M., Ross, I. L., Wolf, P. S. A., & Thomas, K. G. F. (2017). Impaired quality and efficiency of sleep impairs cognitive functioning in Addison's disease. *Psychoneuroendocrinology*, 78, 237-245. doi: 10.1016/j.psyneuen.2017.02.004
- d. Henry, M., Thomas, K. G. F., & Ross, I. L. (2018). Reduced slow-wave sleep in patients with Addison's disease. *European Journal of Endocrinology*. Manuscript revised and resubmitted and awaiting reviewer feedback.

To the best of my knowledge and belief this dissertation contains no material written by another person (except where due acknowledgement has been made regarding peer-reviewed journal papers published by myself and co-authors), nor has the material been submitted in the past for a degree at this University or at any other university.

Signed by candidate

Michelle Henry

23 July 2018

Date

“Sleep is that golden chain that ties health and our bodies together”

~ Thomas Dekker (December 28, 1987)

“Early to bed and early to rise makes a man healthy, wealthy and wise”

~ Benjamin Franklin (January 17, 1706)

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Abbreviations

ACTH	Adrenocorticotrophic hormone
AD	Addison's disease
ANOVA	Analysis of variance
AVLT	Auditory-Verbal Learning Test
BDI-II	Beck Depression Inventory II
BMI	Body mass index
BTACT	Brief Test of Adult Cognition by Telephone
CAR	Cortisol awakening response
CFQ	Cognitive Failures Questionnaire
CRH	Corticotropin-releasing hormone
EEG	Electroencephalograph
ESE	Effect size estimate
FTT	Finger Tapping Task
GC	Glucocorticoid
GH	Growth hormone
GHRH	Growth hormone-releasing hormone
GR	Glucocorticoid receptor
HPA	Hypothalamic-pituitary-adrenal
LM	Logical Memory
MINI	Mini International Neuropsychiatric Interview
MR	Mineralocorticoid receptor

N1	Non-rapid eye movement sleep stage 1
N2	Non-rapid eye movement sleep stage 2
NREM	Non-rapid eye movement
PFC	Pre-frontal cortex
PGO	Ponto-geniculo-occipital
PSG	Polysomnography/polysomnographic
PSQI	Pittsburgh Sleep Quality Index
RAVLT	Rey Auditory-Verbal Learning Test
REM	Rapid eye movement
SAAD	South Africans Addison's disease
SF-36	Short-Form 36
SWS	Slow-wave sleep
TST	Total sleep time
WASO	Wake after sleep onset

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Abstract

Recent literature in the neurosciences suggests that there are mechanistic relations between sleep disruption and cognitive (particularly memory) deficits, and that varying concentrations of the hormone cortisol may play a particularly important role in mediating those relations. Because patients with Addison's disease (AD) experience consistent and predictable periods of sub- and supra-physiological cortisol concentrations (due to lifelong glucocorticoid replacement therapy), and because they frequently report disrupted sleep and poor memory, those presenting with that endocrinological disorder form an ideal population to use in studies testing hypotheses about the ways in which (a) disrupted sleep is related to impaired consolidation of previously learned material (and, hence, poor performance on tests assessing memory for that material), and (b) cortisol concentrations may mediate this relationship between sleep and memory. This dissertation presents four studies that, together, tested those hypotheses. Study 1 ($n = 60$ per group) found that patients with AD self-reported significantly more disturbed sleep and poorer cognition and quality of life compared to matched healthy controls. Importantly, our analyses suggested that disrupted sleep, and not AD per se, accounted most strongly for the reported cognitive impairment. Study 2 ($n = 35$ per group) found that patients had significantly poorer objectively-measured declarative memory performance compared to matched healthy controls, but that other domains of cognition were relatively unimpaired. Study 3 ($n = 10$ per group) suggested that matched healthy controls retained significantly more declarative information than patients. Importantly, while controls retained significantly more declarative information when a period of sleep, rather than waking, separated learning from recall, patients derived no such benefit. Study 4 ($n = 7$ per group) suggested that, relative to matched healthy controls, patients had different patterns of night-time cortisol secretion, accompanied by significantly reduced slow-wave sleep. Together, these four studies suggest that, despite being on replacement

medication, patients with AD still experience disrupted sleep and memory deficits. These disruptions and deficits may be related to the failure of replacement regimens to restore a normal circadian rhythm of cortisol secretion. This pattern of results provides support for existing theoretical frameworks which posit that (in AD and other neuroendocrine, neurological, or psychiatric disorders) disrupted sleep is an important biological mechanism that underlies, at least partially, the memory impairments that patients frequently report experiencing. With specific regard to patients with AD, the findings presented here suggest that future initiatives aimed at improving patients' cognitive performance (and, indeed, their overall quality of life) should prioritise optimizing sleep. More generally, this dissertation advances our understanding of sleep as a critical biological process essential for cognitive well-being.

CHAPTER ONE:

GENERAL INTRODUCTION

Sleep is a critical biological process, an inevitable and essential aspect of normal human physiology. Nonetheless, questions about the function(s) of sleep (e.g., whether it is necessary for more than simple physical and mental restoration) remained unanswered until relatively recently. Current neuroscience literature provides some of the sought-for answers, suggesting that healthy, uninterrupted sleep is vital to ensuring that consolidation of memory traces acquired during waking hours occurs smoothly and efficiently. Furthermore, it appears that the hormone cortisol plays a particularly important role in mediating the sleep-memory relationship.

Patients with AD must be on lifelong glucocorticoid replacement therapy and, consequently, experience periods of sub- and supra-physiological cortisol concentrations. Because of these disruptions to the normal circadian rhythm of cortisol, studies of these patients provide a unique opportunity to investigate the relationship between sleep and memory.

Hence, a key concern for the current research is that alterations in cortisol concentrations may disrupt sleep architecture (because cortisol is involved in the initiation and maintenance of the various stages of sleep across the night), and, consequently, cognitive performance (because the successful initiation of, and transitions between, sleep stages both play a vital role in the memory consolidation process). Furthermore, the action of cortisol at hippocampal receptor sites means that the hormone has a direct influence on the process of memory consolidation, much of which takes place during sleep.

Although most research on AD subjects' well-being focuses on quality of life, specifically that related to physical health and vitality, several studies indicate that patients with AD report experiencing both sleep disruptions and memory deficits. One possible, but

yet to be explored, explanation for this pattern of data is that the periods of sub- and supra-physiological cortisol concentrations experienced by patients with AD may have a specific negative impact on processes of sleep-dependent memory consolidation.

Hence, the overall aim of the research programme described in this doctoral dissertation is to investigate the broad hypotheses that (a) disrupted sleep is a vital mechanism underlying the impaired consolidation of previously learnt information, and (b) the relationship between sleep and successful memory consolidation is mediated by normal circadian rhythms of cortisol. This dissertation presents a series of four studies that, together, investigated that aim. Study 1 aimed to characterise self-reported quality of life in a sample of South African patients with AD, and to investigate whether memory complaints reported by patients are associated with subjectively-measured sleep disruptions. Study 2 aimed to investigate whether subjective cognitive deficits in patients with AD, as reported in previously published studies, are confirmed by objective measures of cognitive performance. The study quantifies and describes the functioning of patients with AD across a variety of cognitive domains (e.g., processing speed, attention, declarative memory, executive functioning), and compares their cognitive performance to that of healthy controls. Study 3 aimed to quantify and describe objectively measured sleep quality and objective memory performance in a sample of patients with AD and matched healthy controls, and to investigate whether disrupted sleep is a possible mechanism underlying memory impairment in those patients. Otherwise stated, this study aimed to explore whether sleep augments memory consolidation in patients as it is known to do in healthy individuals. Finally, because specific disruptions to the normal architectural distribution of sleep could be a possible mechanism underlying memory disturbances, and may, in turn, be linked to altered cortisol rhythmicity, Study 4 investigated the relationship between polysomnographic measures of sleep and their

relationship with night-time cortisol secretion in patients with AD compared to matched healthy controls.

In summary, the primary focus of this PhD research is on the relationships between sleep disruption, sub- and supra-physiological cortisol concentrations, and memory functioning. I used patients with AD to explore these relationships because, despite being on replacement medication, these individuals experience non-physiological cortisol concentrations, particularly during the night, and frequently report disrupted sleep and poor memory. Broadly speaking, then, this dissertation seeks to bolster the growing amount of scientific evidence suggesting that sleep is a critical biological process whose functional value extends well beyond simple physical and mental restoration.

CHAPTER TWO:

LITERATURE REVIEW

Sleep

Sleep is a natural state of reduced responsiveness to external stimuli. Human sleep, which is usually accompanied by a loss of consciousness, is regulated by three different processes: the homeostatic process that determines its need, the circadian process that determines sleep timing, and the ultradian process that determines its organisation (Borbély, Daan, Wirz-Justice, & Deboer, 2016; Vassalli & Dijk, 2009). Homeostatic sleep pressure increases as a person stays awake, and eventually results in that individual falling asleep (Blaivas, Patel, Hom, Antigua, & Ashtyani, 2007; Borbély et al., 2016; Harrison & Horne, 1996). Regarding the circadian clock, its timing mechanism is located in the suprachiasmatic nucleus (SCN) and incorporates three different components: (1) input pathways that transmit light and other environmental signals to the clock, (2) an endogenous pacemaker that generates 24-hour rhythms, and (3) output pathways that project to other brain regions and peripheral organs (Borbély et al., 2016; Dibner, Schibler, & Albrecht, 2010). The circadian clock is responsible for daily variations in body temperature, melatonin, and cortisol secretion, and will align those rhythms with those of sleep and other physiological processes (Partch, Green, & Takahashi, 2014; Takahashi, 2017). For example, body temperature and cortisol reach a nadir in the late night, promoting sleep onset and duration, whereas melatonin rises during the night to promote sleep. During sleep, ultradian rhythms determine the repetitive cycles of rapid eye movement (REM) and non-REM (NREM) throughout the night (Chokroverty, 2017).

Structure of sleep. In mammals, sleep is divided into two main categories: REM and NREM. Human sleep is cyclical in nature, alternating between 4-6 repeated cycles of REM and NREM sleep, with each cycle lasting approximately 90-120 minutes (Carskadon &

Dement, 2011; Chokroverty, 2017; Markov & Goldman, 2006). NREM sleep is divided into four stages, with slow-wave sleep (SWS) being the deepest of the NREM stages. The majority of SWS (up to 80%) occurs during the first half of a typical 8-hour night, whereas the second half of the night contains twice as much REM sleep as the first (Chokroverty, 2017; Markov & Goldman, 2006). This preferential distribution of SWS in the first half of the night is thought to be a response to the length of prior wakefulness, and reflects the homeostatic need for sleep (that is to say, it is highest at sleep onset and diminishes as sleep pressure declines; Carskadon & Dement, 2011; Fang & Rao, 2017).

Each stage of sleep is defined by characteristic electroencephalograph (EEG) frequencies and wave-forms that relate to different levels of arousal and neuronal synchronicity¹ (Diekelmann & Born, 2010). Higher EEG frequencies (e.g., in the beta band, > 13 cycles/sec) are associated with wakefulness, whereas decreases in frequency (e.g., in the alpha (8-13 cycles/sec), theta (4-7 cycles/sec, and delta (< 4 cycles/sec) occur with increasing depth of sleep (Carskadon & Dement, 2011). These characteristic EEG frequencies and waveforms are shown in Figure 1.1. Stage 1 (N1) sleep is a transitional state between wakefulness and sleep, and is characterised by mixed frequency EEG and theta waves, as well as slow rolling eye movements and a slight reduced muscle tone. Stage 2 (N2) is a light form of sleep and is characterised by mixed frequency EEG in combination with sleep spindles and K-complexes. SWS contains slow brain oscillations (0.5-1Hz) and delta activity (1-4Hz) and is made up a combination of Stage 3 (N3; where 20-50% of the waveforms are delta) and Stage 4 (N4; where more than half of the waveforms are delta) sleep. During this stage, heart rate and breathing slows down (Fogel & Smith, 2011; Steriade, 2006). REM sleep is characterised by a mixed-frequency EEG, with theta or sawtooth waves, rapid eye

¹ Neuronal synchrony is the simultaneous oscillations of membrane potentials in a network of neurons, resulting in synchronous firing patterns in the network.

movements, and a nearly absent chin muscle tone. REM sleep is also known as paradoxical sleep because it is characterised by CNS activation that resembles wakefulness, a reduced arousal threshold, and increased mental activity associated with dreaming (Nielsen, 2000; Ravassard, Hamieh, Malleret, & Salin, 2015).

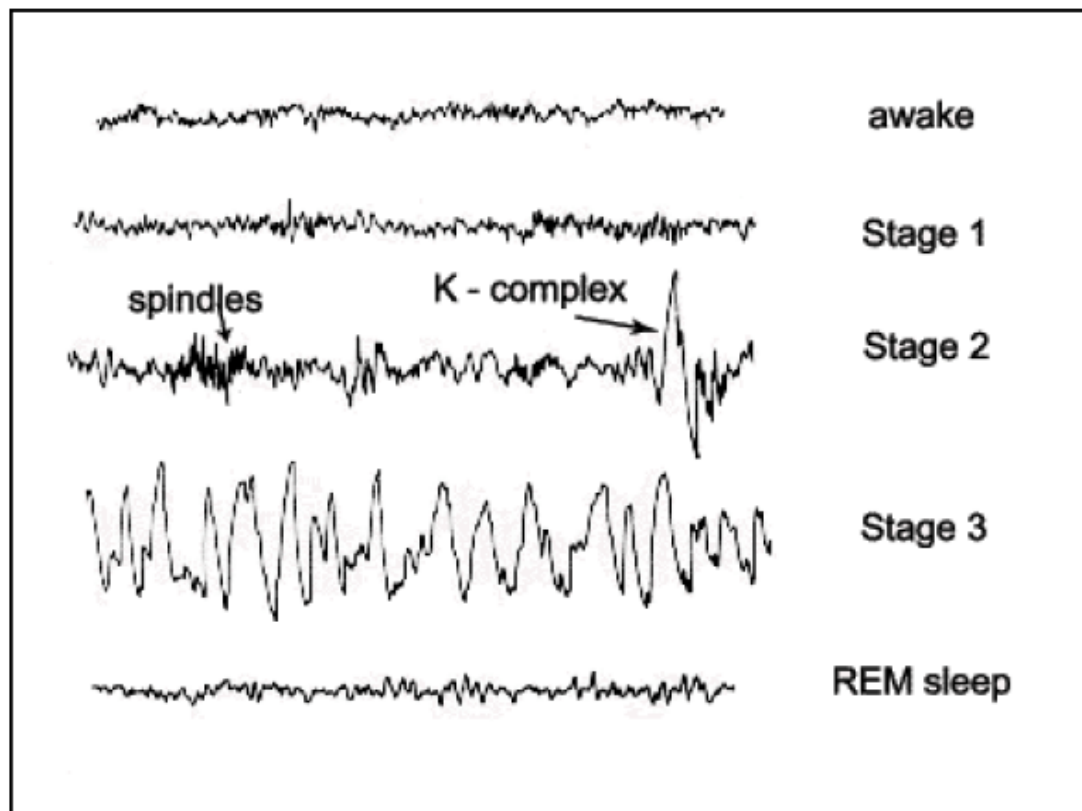


Figure 1.1. EEG frequency and wave forms of different sleep stages, as measured by a polysomnograph recording. From: Šušmáková, K. (2004). Human sleep and sleep EEG. *Measurement Science Review*, 4(2), 59-74.

Human sleep patterns have some reliable characteristics (see Figure 1.2). Sleep onset is characterised by rhythmic alpha waves, occurring particularly in the occipital regions. Sleep then begins with NREM and progresses through deeper NREM stages before the first episode of REM. The first sleep cycle usually begins with N1, which lasts for 1-7 minutes after sleep onset. N2, which lasts for 10-25 minutes, is signalled by K-complexes. As N2 progresses, high-voltage slow-waves appear, signalling the start of SWS. Within SWS, N3 lasts only a few minutes, whereas N4 lasts for 20-40 minutes. The body may re-enter lighter

stages of sleep (N1-N3) for ~5 minutes before the first REM episode is initiated. This episode is short-lived, lasting only 1-5 minutes. Thereafter, NREM and REM continue to alternate in a cyclic manner throughout the night, with REM cycles becoming longer and SWS shorter as the night progresses. Brief waking episodes tend to intrude in the later night, usually near the transitions into REM sleep (Markov & Goldman, 2006).

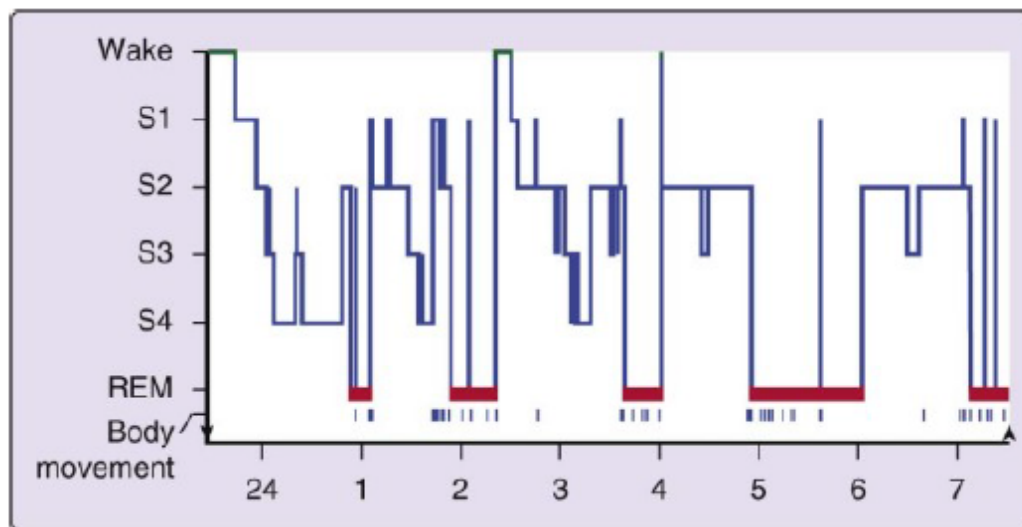


Figure 1.2. This hypnogram illustrates the progression of sleep stages across a single night in a normal volunteer. From: Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep*, 27(7), 1255-1273.

Overall, Stage 1 generally constitutes 2-5% of the night's sleep, Stage 2 45-55%, SWS 13-23%, REM 20-25%, and wakefulness around 5% (Carskadon & Dement, 2011). Total length of sleep is highly variable from person to person and night to night, although most young adults report 7.5-8.5 hours of sleep per night (Hirshkowitz et al., 2015). Sleep length and tendencies also depends on genetic factors, volitional factors (staying awake late, waking by alarm clock) and, importantly for this dissertation, circadian rhythms (Carskadon & Dement, 2011; Fang & Rao, 2017; Gottlieb, O'Connor, & Wilk, 2007; Klei et al., 2005).

Circadian Rhythmicity: The Control of Hormone Release

The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the body's homeostatic processes, sleep regulation, and in the co-ordination of an organism's ability to cope with environmental stressors. It accomplishes the latter by increasing the amount of readily available energy, increasing cardiovascular tone, and altering cognition (Gjerstad, Lightman, & Spiga, 2018; Lightman & Conway-Campbell, 2010; Oelkers, 1996; Rosmond & Björntorp, 2000; Sapolsky, Krey, & McEwen, 1986). This physiological system regulates the secretion of various hormones, one of which is cortisol, a corticosteroid hormone secreted from the adrenal glands. The system is activated by a circadian pacemaker or in response to stress.

When the brain perceives the presence of a stressor (a physical or psychological threat to the organism's integrity; Kemeny, 1994), a two-armed physiological stress response, aimed at enabling the body to adapt to that disturbance and restore homeostasis, is evoked (de Kloet, Vreugdenhil, Oitzl, & Joels, 1998; Herman et al., 2016; Lightman & Conway-Campbell, 2010). One arm of the physiological stress response (the fast, immediate response that resolves quickly) is centred on the sympathetic nervous system, and after a neuroendocrine release, results (in humans) in the secretion of catecholamines (norepinephrine and epinephrine). The other arm of the responses (the slower response that resolves over a longer period) is centred on the HPA axis, and is associated with its own unique neuroendocrine release (Herman et al., 2016).

To wit: The perception of a stressor triggers the release of corticotrophin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus. This release, in turn, triggers the anterior pituitary to release adrenocorticotrophic hormone (ACTH). That release, in turn, results in the secretion of glucocorticoids (GCs; in humans, the primary GC is cortisol) from the adrenal gland. GC levels exert negative feedback on the hypothalamus and

pituitary gland, thereby controlling the synthesis and release of CRH, ACTH, and growth hormone (GH; Buckley & Schatzberg, 2005; Gjerstad et al., 2018; Herman et al., 2016; Oster et al., 2006; Walker, Terry, & Lightman, 2010). In this way, exogenous stressful events, or stress-provoking mental events, trigger the secretion of cortisol and controls concentrations of the hormone. However, the biggest endogenous stimulus for the secretion of cortisol (and other hormones) is circadian rhythmicity.

The release of nearly all hormones is characterised by daily oscillations (periodic pulsatile bursts), which result from an interaction between circadian rhythmicity (biological processes that have endogenous oscillations of around 24 hours) and the sleep-wake cycle (Borbély et al., 2016; Van Cauter & Turek, 2000; Van Reeth et al., 2000; Vgontzas & Chrousos, 2002). Circadian rhythms are generated by an endogenous ‘master clock,’ which is located in the SCN of the hypothalamus, by light, and by ultradian (biological processes that have endogenous oscillations of less than 24 hours) pulsatility (Mistlberger & Rusak, 2005; Pauls, Honma, Honma, & Silver, 2016). This internal master clock ensures we anticipate and prepare for changes in our environment and act appropriately (Chung, Son, & Kim, 2011; Koch, Leinweber, Drengberg, Blaum, & Oster, 2017). For example, as night approaches, cortisol levels and core body temperature decline and melatonin levels increase to prepare our bodies for sleep (Hickie, Naismith, Robillard, Scott, & Hermens, 2013). Circadian oscillators are also located in numerous peripheral tissues, including the liver, lungs, heart, and adrenal glands. These oscillators are synchronised with each other by the master clock (Angelousi et al., 2018). Neurons that make up the master clock in the SCN have their own intrinsic rhythms, which are dependent on the transcription and translation of circadian clock genes (Angelousi et al., 2018; James, Cermakian, & Boivin, 2007). Circadian clock genes (e.g., the Circadian Locomotor Output Cycles Kaput (CLOCK) gene and brain and muscle ARNT-like 1 (BMAL1) gene) play an important role in generating circadian rhythms. Clock genes are

also expressed in peripheral tissues that contain circadian oscillators (Abe et al., 2002; James et al., 2007).

Daily rhythms of HPA-axis hormones. In healthy people without diseases affecting the HPA axis, cortisol has a robust diurnal secretory pattern. The highest concentrations of the hormone occur in the early hours of the morning, with a peak just after waking. Concentrations then decrease slowly throughout the day, with troughs in the mid-afternoon and at midnight, and the daily nadir several hours after initiation of nocturnal sleep. Cortisol levels begin to rise from 02h00 to 03h00, and continue to rise until awakening. The nocturnal rise in cortisol and early morning peak in HPA activity is thought to reflect the increasing energy demands of the brain towards the end of the night (Benedict et al., 2009; Hirotsu, Tufik, & Andersen, 2015; Steiger, 2002, 2007). Thereafter, the day-long decline in cortisol levels may represent the recovery of the HPA axis from this early-morning endogenous challenge (Balbo, Leproult, & Van Cauter, 2010).

The daily rhythm of CRH and ACTH occur in close parallel with the daily rhythm of cortisol, all highest in the morning and reaching a nadir during early sleep (Chokroverty, 2017; Steiger, 2003, 2007). In contrast, melatonin (secreted from the pineal gland and synchronised to light via input from the retinas) and GH are high during early sleep, suggesting a reciprocal relationship between the HPA and hypothalamo-pituitary-somatotrophic (HPS) systems (Angelousi et al., 2018).

The HPA axis and sleep. The HPA axis plays an important role in maintaining alertness and modulating sleep (Buckley & Schatzberg, 2005; Chrousos, Vgontzas, & Kritikou, 2016; Hirotsu et al., 2015). A bidirectional relationship exists between sleep architecture and the HPA axis: the hormones governing that system (both endogenous and exogenously administered) exert specific effects on sleep, whereas changes to sleep affect secretion of these hormones (Steiger, 2002, 2007; van Dalsen & Markus, 2017).

Endogenous HPA hormones and their effect on sleep. The circadian rhythmicity of specific hormones plays an essential role in sleep timing and offset, and in the distribution of sleep stages across the night (Buckley & Schatzberg, 2005; Dijk & Lockley, 2002; Skeldon, Derks, & Dijk, 2016; Steiger, 2002). Inhibitory HPA-axis mechanisms (particularly during SWS) are responsible for attenuated cortisol activity during the first half the night. The quiescent period of HPA-axis activity starts before sleep onset, and continues into the first half the night when SWS occurs to its greatest degree. Cortisol levels decrease rapidly in the first 20 minutes after SWS onset, and there is a consistent temporal relationship between low cortisol and high SWS (Balbo et al., 2010; Born, Späth-Schwalbe, Schwakenhofer, Kern, & Fehm, 1989; Follenius, Brandenberger, Badesapt, Libert, & Ehrhart, 1992; Hirotsu et al., 2015; Neylan et al., 2003; Van Reeth et al., 2000). Optimal cortisol levels experienced during early sleep probably enhance SWS through feedback inhibition of CRH (Buckley & Schatzberg, 2005; Steiger, 2002).

In the second half of the night, when REM predominates, inhibitory mechanisms are weakened and HPA secretory activity slowly increases (Born, Schenk, Späth-Schwalbe, & Fehm, 1988; Van Reeth et al., 2000). Cortisol, CRH, and ACTH secretion and sympathetic system activity increase during the latter part of the night, and an increase in cortisol paired with an increase in REM during the last sleep cycle has been reported (Fehm, Späth-Schwalbe, Pietrowsky, Kern, & Born, 1993). In summary, while the deepening of sleep is associated with decreasing cortisol levels and decreased sympathetic tone, high autonomic and high cortisol activity occur during REM cycles (Steiger, 2002, 2007).

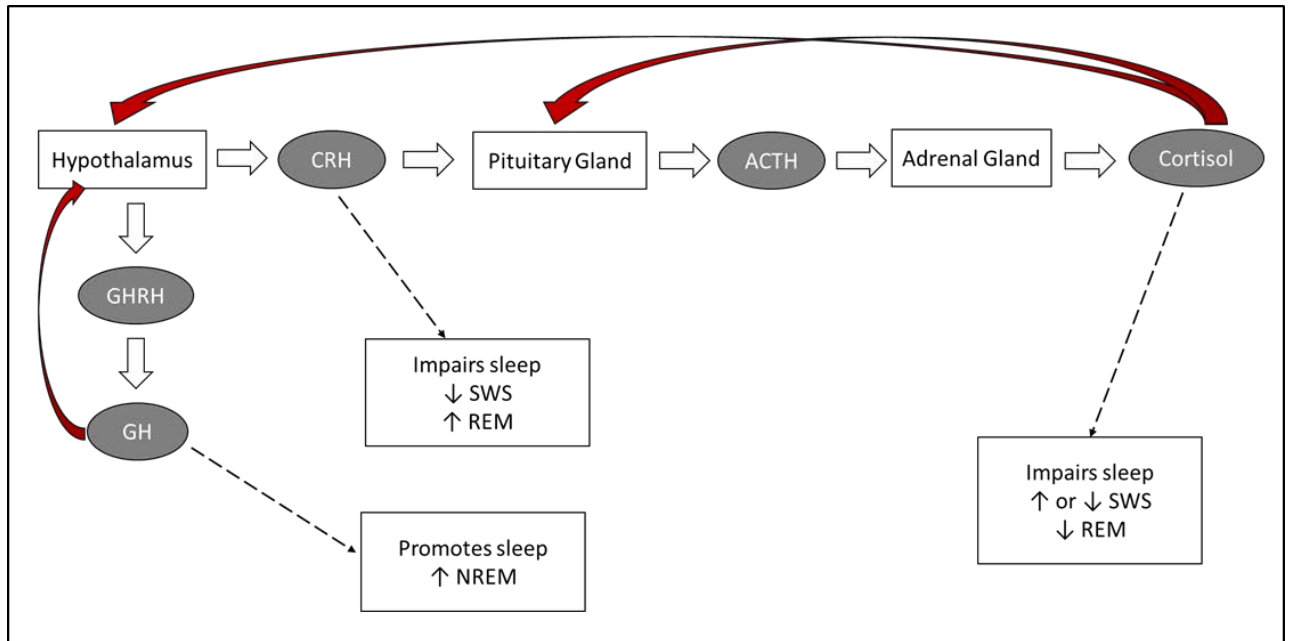


Figure 1.3. The hormonal control of sleep. Red arrows: negative feedback on the indicated brain structure.

The reciprocal relationship between growth-hormone releasing hormone (GHRH) and CRH also plays an important role in regulating sleep. Whereas higher levels of GHRH are associated with HPA-axis activity during early sleep, stimulating NREM and promoting sleep, higher levels of CRH are associated with inhibition of SWS, enhancement of REM and vigilance, and disruption of sleep (Chang & Opp, 2001; Schüssler et al., 2016; Steiger, 2003, 2007; Vgontzas, Bixler, Wittman, et al., 2001). This pattern points to a reciprocal interaction between sleep architecture and hormones of the hypothalamic-pituitary-somatotrophic (HPS) and HPA systems. Confirming the sleep-promoting role of GHRH and the sleep-disrupting effect of CRH, in older adults the typical age-related reduction in GH levels is accompanied by reduced SWS, whereas in both older adults and in depressed younger adults increased CRH levels contribute to the typically-observed sleep disruptions (Steiger, 2003; Steiger, Pawlowski, & Kimura, 2015; Van Coevorden et al., 1991).

Finally, ACTH and melatonin also play a role in sleep regulation. ACTH affects sleep because it is a primary stimulus for night-time cortisol secretion (Born et al., 1989; Chorous

et al., 2016; Steiger & Holsboer, 1997). Similarly, the release of melatonin (which has a sleep-promoting effect) has a clear circadian rhythm, with maximal secretion during the night and (Brzezinski et al., 2005; Cajochen, Kräuchi, & Wirz-Justice, 2003). In fact, melatonin can induce sleep even when the homeostatic drive to sleep is insufficient. Hence, melatonin administration has been used to treat insomnia and circadian rhythm disorders as it can inhibit the drive for wakefulness and induce phase shifts in the circadian clock so that sleep occurs at a desired time (Cajochen et al., 2003; Zhdanova et al., 1995).

Effects of exogenous administration of HPA hormones and their impact on sleep. A relatively large literature suggests that exogenous administration of HPA hormones and their antagonists modulate sleep (Buckley & Schatzberg, 2005; Chorous et al., 2016; Steiger, 2002, 2003, 2007).

Regarding cortisol, excessively high endogenous concentrations of this hormone (such as those present in depression and Cushing's disease) are associated with more night-time awakenings, an increased percentage of light sleep and REM, and a reduction of SWS percentage (Armitage, Emslie, Hoffmann, Rintelmann, & Rush, 2001; Hirotsu et al., 2015; Shipley, Schteingart, Tandon, & Starkman, 1992; Steiger, 2003). In one study confirming that high cortisol concentrations are associated with reduced SWS, Vgontzas and colleagues (2001) found that after administration of CRH, higher cortisol levels during the first half of the night were associated with reduced SWS in middle-aged men (although it should be noted that sleep and cortisol could have been affected by CRH independently). Similarly, Neylan and colleagues (2003) found that high cortisol and ACTH levels were associated with a reduction in SWS in healthy controls after administration of metyrapone. However, in contrast to the literature showing that high cortisol concentrations reduce SWS and increase REM, continuous and pulsatile night-time infusion of cortisol has been shown to increase SWS and decrease REM in both young and elderly healthy men (Bohlhalter, Murck,

Holsboer, & Steiger, 1997; Born, DeKloet, Wenz, Kern, & Fehm, 1991; Friess, Bardeleben, Wiedemann, Lauer, & Holsboer, 1994; Friess, Tagaya, Grethe, Trachsel, & Holsboer, 2004). Several studies have also confirmed that, in healthy adults, higher evening cortisol concentrations are associated with a reduction in REM² (Bohlhalter et al., 1997; Born et al., 1991; Fehm et al., 1993; Friess et al., 1994; Van Cauter, Leproult, & Plat, 2000), and that exogenous administration of cortisol or ACTH administration (which increases cortisol concentrations) are associated with the suppression of REM (Born et al., 1989; Fehm et al., 1993; Gillin, Jacobs, Snyder, & Henkin, 1974a; Vgontzas, Bixler, Wittman, et al., 2001; Vgontzas et al., 2003). This inhibition of REM sleep in healthy individuals may be related to the negative feedback of GCs on the HPA axis (Garcia-Borreguero et al., 1994; Gillin et al., 1972). The discrepancy in results between endogenous and exogenously administered cortisol on sleep could be because synthetic versus natural steroids exert different effects on HPA hormones and on sleep, or because short-term administration of exogenous cortisol³ has different effects on sleep compared to continuous endogenously elevated concentrations of cortisol. For example, endogenous cortisol elevations are associated with an increase in CRH, whereas pharmacological glucocorticoid treatment that increases cortisol inhibits the HPA axis and reduces CRH secretion (Bennion, Mickley Steinmetz, Kensinger, & Payne, 2015).

Sleep literature proposes two other possible explanations for the above-mentioned discrepancy. First, the effects of exogenous HPA hormones on sleep is modulated by the relative occupation of MR and GR receptors. Specifically, GCs inhibit or enhance SWS depending on whether MRs or GRs are primarily activated. In this dose-dependent effect,

² The REM outcome variable I am referring to here is REM percentage (i.e. the proportion of total sleep spent in REM), not REM density (the frequency of rapid eye movements during REM sleep). The reason for this distinction is because several show that exogenous administration of CRH (Holsboer, Von Bardeleben, & Steiger, 1988), prednisone (Gillin, Jacobs, Fram, & Snyder, 1972), and hydrocortisone (Garcia-Borreguero, Schwartz, Barker, Barbato, & Wehr, 1994) reduce the proportion of REM sleep but not REM density.

³Cortisol can often have a relatively slow onset of effects, and as such, we would expect that temporal correlations show a time lag.

lower cortisol concentrations that primarily occupy MR's promote SWS, whereas higher cortisol concentrations that primarily occupy GR's reduce SWS (Born et al., 1989; Hirotsu et al., 2015). Second, recent studies suggest that the effects of corticosteroids on sleep depend on HPA-axis feedback inhibition of CRH (which inhibits SWS and enhances REM). It has therefore been proposed that the effects of both endogenous and exogenous cortisol on SWS depend on whether optimal cortisol levels are reached to suppress nocturnal CRH (Buckley & Schatzberg, 2005).

Regarding the occupation of different types of receptors, it has been suggested by Born and colleagues that the occupation of MRs may have implications for SWS, whereas the occupation of GRs may have implications for REM sleep. Confirming this suggestion, a series of studies using healthy human adults as participants showed that when cortisol activated MRs SWS increased, whereas occupation of GRs following the administration of dexamethasone or cortisol reduced REM (Born et al., 1991).

Regarding feedback inhibition of CRH, low concentrations of cortisol (as are present during early sleep) that occupy high-affinity MR's exert inhibitory feedback on CRH (particularly via the hippocampus). This MR-mediated suppression of CRH may explain why SWS is more prominent during the first half of the night. On the other hand, high concentrations of cortisol (as are present during the second half sleep, particularly in the late night and early morning) that occupy low-affinity GRs can exert inhibitory (via the paraventricular nucleus) or excitatory (via the amygdala) feedback on CRH (Buckley & Schatzberg, 2005). This excitatory feedback might explain why there is relatively less SWS and relatively more REM sleep during the second half of the night. The inhibitory feedback might explain why several studies have found that high cortisol levels reduce REM.

Regarding exogenous administration of CRH, repetitive hourly intravenous (IV) infusions of CRH have been shown to decrease SWS, decrease REM, and increase cortisol

levels during the first half of the night (Holsboer et al., 1988). Similarly, IV infusion of CRH increases light sleep (Stage 1 and 2), and decreases SWS and sleep efficiency (Tsuchiyama, Uchimura, Sakamoto, Maeda, & Kotorii, 1995). However, other studies have reported that neither continuous IV infusions or hourly IV injections of CRH effect sleep EEG (Born et al., 1989; Kellner et al., 1997). In attempting to explain these discrepancies, Vgontzas et al. (2001) suggested that the responsiveness of sleep patterns to CRH could be age dependent: Whereas a single dose of CRH given to young men does not change EEG patterns, the same dose given to middle-aged men increases wakefulness and decreases SWS.

Regarding exogenous administration of ACTH, continuous nocturnal IV infusions of ACTH have been shown to decrease REM sleep and result in increased cortisol and GH (Born et al., 1989; Fehm et al., 1993; Gillin et al., 1974a). On the other hand, IV pulsatile nocturnal administration of a synthetic ACTH analogue has been shown to increase sleep latency and wakefulness, decrease sleep efficiency, and reduce SWS (during early sleep), while leaving secretory patterns of cortisol and GH unchanged (Steiger et al., 1991). Contrary to the above studies, Kellner and colleagues demonstrated that hourly IV injections of ACTH administered throughout the day had no effect on sleep EEG, while significantly elevating cortisol. Therefore, literature on the effects of exogenous administration ACTH on sleep are quite inconsistent.

In summary, literature on the effects of exogenous administration of HPA-axis hormones on sleep show some complimentary and contradictory findings. Although elevated cortisol concentrations generally reduce REM and enhance SWS, this relationship is mediated by whether optimal cortisol levels are reached to suppress CRH, and the relative occupation of MR and GR receptors.

Effects of sleep on HPA hormones. Sleep appears to have a direct impact on cortisol secretion. Specifically, sleep onset is associated with inhibitory effects on cortisol secretion,

effects that persist for 1-2 hours post-onset (Balbo et al., 2010; Van Cauter & Refetoff, 1985). In contrast, awakenings and sleep offset are accompanied by cortisol stimulation (Chorous et al., 2016; Späth-Schwalbe, Gofferje, Kern, Born, & Fehm, 1991). Nocturnal awakenings, in particular, appear to provoke pulsatile secretions of cortisol, followed by a temporary inhibition of cortisol secretion (Balbo et al., 2010; Chang & Opp, 2001; Späth-Schwalbe et al., 1991).

Like nocturnal awakenings, final morning awakening elicits a rapid and marked increase in both ACTH and cortisol. Unlike nocturnal awakenings, however, this cortisol awakening response (CAR), which includes a 50-60% increase in cortisol secretion, lasts about an hour, with a peak at about 30 minutes post-awakening (Kirschbaum & Hellhammer, 2000; Pruessner et al., 1997; Smyth, Thorn, Hucklebridge, Evans, & Clow, 2015; Steptoe & Serwinski, 2016). Some research suggests that the secretion of ACTH and cortisol during late sleep is precipitated by the physiological expectation that sleep will end at a certain time, and/or by the anticipation of the stress of waking (Born, Hansen, Marshall, Mölle, & Fehm, 1999; Clow, Hucklebridge, Stalder, Evans, & Thorn, 2010; Fries, Dettenborn, & Kirschbaum, 2009).

Exaggeration or blunting of the CAR has been associated with a variety of psychiatric and medical conditions including depression (Bhagwagar, Hafizi, & Cowen, 2005; Dedovic & Ngiam, 2015; Huber, Issa, Schik, & Wolf, 2006; Stetler & Miller, 2005; Vrshek-Schallhorn et al., 2013), PTSD (Chida & Steptoe, 2009; Pinto, Correia-Santos, Costa-Leite, Levendosky, & Jongenelen, 2016; Wessa, Rohleder, Kirschbaum, & Flor, 2006), burnout (Grossi et al., 2005; Oosterholt, Maes, Van der Linden, Verbraak, & Kompier, 2015), and chronic fatigue (Roberts, Wessely, Chalder, Papadopoulos, & Cleare, 2004; Tak et al., 2011). Outside of such conditions, the morning CAR is fairly consistent and robust, and is unaffected by age (Pruessner et al., 1997; Wust et al., 2000), menstrual cycle phase

(Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Kudielka & Kirschbaum, 2003), use of oral contraceptives (Kirschbaum et al., 1999; Wust et al., 2000) or smoking (Kudielka, Broderick, & Kirschbaum, 2003; Kudielka & Kirschbaum, 2003; Wust et al., 2000).

Effects of sleep disruption on circadian rhythms. Acute shifts in the sleep-wake cycle (such as sleeping during the day instead of the night, or the consequences of jetlag and shift-work), reduced sleep quality, and sleep deprivation all lead to HPA-axis activation, and hence can alter the normal circadian pattern of cortisol secretion (Balbo et al., 2010; Charles et al., 2016; Goichot et al., 1998; Hung, Aronson, Leung, Day, & Tranmer, 2016; Klumpers et al., 2015; Späth-Schwalbe, Schöller, Kern, Fehm, & Born, 1992; Wright Jr et al., 2015).

Regarding acute shifts in the sleep-wake cycle, studies of shift-workers (e.g., those with atypical work schedules that might feature early starts, extended shifts, or night-time labour) have shown a lack of entrainment of cortisol to a night-orientated work schedule both after short (i.e., 1-2 nights) and after more prolonged periods of shift-work (Boivin & Boudreau, 2014). Specifically, cortisol continues to peak in the early hours of the morning and at night (whereas in healthy individuals, cortisol levels are minimal during these times). Furthermore, cortisol is higher during daytime sleep episodes than during normal nocturnal sleep, and lower during night-time compared to daytime wake periods, reflecting a reversal of the normal circadian rhythm (Weibel & Brandenberger, 1998). Along with these alterations in the normal circadian rhythm of cortisol secretion, studies report that shift-workers experience sleep disruptions and/or excessive sleepiness (partly due to the inability to achieve adequate amounts of sleep; Åkerstedt, Nordin, Alfredsson, Westerholm, & Kecklund, 2010; Boivin & Boudreau, 2014; Boivin, Boudreau, James, & Kin, 2012; Morris, Purvis, Mistretta, & Scheer, 2016; Paech, Jay, Lamond, Roach, & Ferguson, 2010).

Regarding poor sleep quality, its experience (and, in fact, even its mere perception) is associated with increases in basal cortisol levels. Such increases stimulate arousal and suppress sleepiness, thus increasing sleep disturbances (which, in empirical studies, are characterised by increased wake time and reduced REM sleep; Chrousos & Gold, 1992; Hirotsu et al., 2015; Vgontzas & Chrousos, 2002; Vgontzas et al., 2003).

Regarding sleep deprivation, several studies report that elevated cortisol levels are present during both the sleep deprivation period (SDP) and the subsequent day and evening (Chapoutot, Buguet, Gronfier, & Brandenberger, 2001; Leproult, Copinschi, Buxton, & Van Cauter, 1997; Meerlo, Koehl, Van der Borght, & Turek, 2002; Minkel et al., 2014; Steiger, 2002; Treuer, Norman, & Armstrong, 1996; Wright Jr et al., 2015). Some researchers explain this physiological pattern by speculating that the initial SDP activates the HPA axis as part of the stress response and may also reflect a decrease in the negative feedback regulation of the HPA axis. Thereafter, prolonged wakefulness increases sleep pressure (the increased need to sleep after periods of wakefulness), leads to fatigue and sleepiness, and causes a blunting of HPA axis activity (Balbo et al., 2010).

However, sleep disruptions do more than just impact the circadian rhythm of HPA-axis hormones. Disrupted sleep has detrimental effects on health/quality of life, mood and cognition, which is not surprising given the central role of sleep in physiological restorative processes, emotion regulation and memory consolidation (Diekelmann & Born, 2010; Guzman-Marin & McGinty, 2006; Hirotsu et al., 2015; Vassalli & Dijk, 2009).

Sleep and Health

When the highly complex and organised physiological process that is sleep is disrupted, the organism is at risk of ill-health and, in some instances, even death (Anothaisintawee, Reutrakul, Van Cauter, & Thakkinstian, 2016; Drake, Roehrs, & Roth,

2003; Luyster, Strollo, Zee, & Walsh, 2012; Reid et al., 2006). Healthy sleep therefore plays an important role in maintaining health, reducing mortality, and increasing longevity.

Insufficient or poor-quality sleep can lead to the development of mental disorders and chronic health conditions by contributing to molecular, immune, metabolic, endocrine and neural changes that play a role in disease development (Chien et al., 2010; Furihata et al., 2015; Hung et al., 2014; Lange, Dimitrov, & Born, 2010; Luyster et al., 2012; J. H. Park, Yoo, & Bae, 2013). For instance, a growing literature reports associations between insufficient amounts of sleep and risk for obesity, Type 2 diabetes, cardiovascular disease, coronary heart disease, and hypertension (e.g., Anothaisintawee et al., 2016; Gangwisch et al., 2006; Gottlieb et al., 2005; Itani, Jike, Watanabe, & Kaneita, 2017; Knutson et al., 2009; Marshall, Glozier, & Grunstein, 2008; Patel & Hu, 2008). Habitually short sleepers also have a greater mortality, possibly because insufficient amounts of sleep contribute to the increased risk for life threatening illnesses such as cardiovascular disease and coronary heart disease (Grandner, Hale, Moore, & Patel, 2010).

Sleep deprivation, and even partial sleep deprivation has negative consequences for health. For instance, healthy adults subjected to partial SDP experience impaired glucose tolerance, higher evening cortisol levels, alterations in SNS activity, reduced leptin, and increased ghrelin (Buxton et al., 2010; Spiegel, Knutson, Leproult, Tasali, & Cauter, 2005). The long-term outcome of SDP is death, with animal studies showing that rats deprived of sleep die within 2-3 weeks (Rechtschaffen & Bergmann, 2002).

However, too much sleep can also lead to health difficulties. For instance, a systematic review and meta-analysis by Jike and colleagues (2017) found that long sleep (greater than 9 hours per night) was significantly associated with increased risk for Type 2 diabetes, cardiovascular disease, stroke, coronary heart disease, and obesity. Longer sleepers also have an increased mortality, which has been linked to increased incidence of

cardiovascular disease with longer sleep duration (Cappuccio, Cooper, D'elia, Strazzullo, & Miller, 2011).

Sleep and quality of life. Literature suggests that poor sleep has a detrimental effect on QoL. These detrimental effects can occur even after a very short period of disrupted sleep. For example, even after just 3 nights of disturbed sleep, otherwise healthy adults report reduced well-being, attention and memory deficits, and irritability (Kunz-Ebrecht, Kirschbaum, Marmot, & Steptoe, 2004). A possible reason why poor sleep has a detrimental effect on QoL is because it reduces life satisfaction. For instance, Zhi et al. (2016) found that, in a sample of 1756 older adults, shorter sleep duration and poorer quality of sleep were associated with lower levels of life satisfaction. Moreover, depression partially mediated the association between short sleep and life satisfaction, and between poor quality sleep and life satisfaction. The authors proposed two mechanisms to explain these findings. First, short and poor-quality sleep could lead to daytime sleepiness, which increases negative emotions and may predispose people to depression (see also Nes et al., 2013). Second, short and poor-quality sleep could be a consequence of poor life satisfaction and depression (see also Koivumaa-Honkanen, Kaprio, Honkanen, Viinamäki, & Koskenvuo, 2004). The latter account is supported by studies showing that people with depression often experience short and disturbed sleep (Armitage, 2007; Armitage et al., 2001; Magee, Caputi, & Iverson, 2011; Pillai, Kalmbach, & Ciesla, 2011).

HPA hormones, sleep, and medical/psychiatric illness. HPA hyperactivity (and consequent elevated cortisol levels, for example) plays an important role in the pathogenesis of medical and psychiatric disorders (e.g., major depressive disorder (MDD), insomnia, and Cushing's disease) that are marked by sleep disturbances (Arnaldi, Mancini, Polenta, & Boscaro, 2004; Balbo et al., 2010; Plat et al., 1999; Sonino, Fava, Raffi, Boscaro, & Fallo, 1998; Spiegel, Leproult, & Van Cauter, 1999). The co-occurring presence of HPA-axis

hyperactivity and sleep disturbance in these disorders is not coincidental. They are directly related, and together constitute a key facet of the clinical manifestation of these disorders.

Both HPA axis and CRH overactivity play a role in the pathophysiology of MDD, meaning that clinically depressed patients experienced elevated cortisol and ACTH throughout the night (Antoničević, Stalla, & Steiger, 2000; Arborelius, Owens, Plotsky, & Nemeroff, 1999; Wong et al., 2000). Although the usual circadian pattern of cortisol is generally preserved in these patients, hyperactivity of the HPA axis is accompanied by alterations in REM sleep (i.e., reduced REM latency, and increased REM percentage and density), increased wakefulness, disturbed sleep continuity, and reduced SWS percentage (or the majority of SWS shifting to the second instead of first half of the night; Armitage et al., 2001; Gold, Goodwin, & Chrousos, 1988).

Patients with insomnia have elevated nocturnal cortisol (particularly in the first half of the night), shorter quiescent periods, and a steeper morning rise in cortisol (Abell, Shipley, Ferrie, Kivimäki, & Kumari, 2016; Rodenbeck & Hajak, 2001; Rodenbeck, Huether, Rüther, & Hajak, 2002; Vgontzas, Bixler, Lin, et al., 2001; Vgontzas et al., 1998). This increased HPA-axis activity promotes sleep fragmentation and nocturnal awakenings, which in turn increases cortisol levels (Rodenbeck & Hajak, 2001; Rodenbeck et al., 2002; Späth-Schwalbe et al., 1991). This vicious cycle may be responsible for the chronicity of insomnia (Abell et al., 2016; Rodenbeck et al., 2002; Vargas et al., 2018).

Patients with Cushing's disease produce excessive amounts of cortisol. This results in the obliteration of the usual circadian rhythm of that hormone (Bierwolf, Kern, Mölle, Born, & Fehm, 2000). Only a few studies have assessed sleep by polysomnography (PSG) in these patients, finding that SWS is decreased, REM latency shortened, REM density is elevated, and aberrances in sleep continuity occur (Krieger & Glick, 1974; Shipley, Schteingart, Tandon, Pande, et al., 1992; Shipley, Schteingart, Tandon, & Starkman, 1992). Shipley and

colleagues (Shipley, Schteingart, Tandon, Pande, et al., 1992) found that elevated cortisol concentrations in 11 patients with Cushing's disease were associated with lower REM activity, and more awakenings during sleep. However, other studies have not directly explored the association between HPA-axis hyperactivity and sleep disturbances in these patients.

The above literature corroborates that HPA activity plays an important role in sleep regulation, and that disruptions to sleep and to the circadian rhythm of cortisol are not coincidentally associated. More specifically, patients with medical or psychiatric conditions that are characterised by elevated cortisol concentrations experience sleep disruptions, including less time in SWS, a shortened REM latency, increased REM sleep and density (particularly in the first half of the night), and sleep discontinuity (Benca, Obermeyer, Thisted, & Gillin, 1992; Wulff, Gatti, Wettstein, & Foster, 2010).

Sleep and Emotion

While it is well established that sleep plays a crucial role in various aspects of health, psychological functioning, and cognition, more recent research has focused on the link between sleep and emotions (Kahn, Sheppes, & Sadeh, 2013; Palmer & Alfano, 2017; Payne & Kensinger, 2010). Sleep plays an important role in the processing and regulation of emotion (Kahn et al., 2013; Palmer & Alfano, 2017; Walker, 2009). A bidirectional relationship exists between sleep and emotion: daytime events, especially those that are emotionally charged (such as stress), have an impact on sleep quality and well-being, whereas the quality and amount of sleep influences ways we react to daytime events (Vandekerckhove & Cluydts, 2010). Specifically, the experience of sleep deprivation or poor sleep quality makes people more sensitive to emotional and stressful events on the following day, elevates negative emotions, and reduces positive emotions (Dagys et al., 2012; Norlander, Johansson, & Bood, 2005; Paterson et al., 2011; Pilcher & Huffcutt, 1996). After

several, or even one night of poor quality sleep we experience emotional changes, including feeling more irritable, angry, and anxious (Bonnet & Arand, 2003; Cluydts, 2003; Lee & Douglass, 2010; Zohar, Tzischinsky, Epstein, & Lavie, 2005). Short sleep duration and poor-quality sleep is also associated with elevated depressive symptoms (Öztürk et al., 2015; Zhai, Zhang, & Zhang, 2015).

A few underlying mechanisms have been identified to explain the relationship between sleep and emotion. The first involves emotional brain networks (such as the medial pre-frontal cortex (mPFC) and amygdala). The amygdala is a crucial brain structure for the encoding of emotional information. It facilitates the initial acquisition of emotional information and tags the emotional memories for future consolidation (Hutchison & Rathore, 2015; McGaugh, 2004). The mPFC regulates the reactivity of the amygdala to emotional information (Phelps, 2006; Strange & Dolan, 2006). Periods of sleep strengthen connectivity between the amygdala and both the hippocampus and the mPFC, thereby enhancing the processing of emotional information (McGaugh, 2004; Sterpenich et al., 2009). Periods of sleep loss have been shown to reduce activity of the mPFC, which results in a decreased ability to inhibit control over negative emotions (Dahl & Lewin, 2002; Yoo, Hu, Gujar, Jolesz, & Walker, 2007). Yoo and colleagues (2007) further demonstrated, using fMRI, that sleep deprived participants show increased amygdala activation in response to negative emotional stimuli, and decreased connectivity between the amygdala and mPFC compared to controls (who had normal amounts of sleep).

REM sleep plays a particularly important role in emotion regulation (Agargun & Cartwright, 2003; Wagner, Hallschmid, Rasch, & Born, 2006; Walker, 2009; Walker & van Der Helm, 2009). Furthermore, clinical studies have implied that patients with nearly all neurological and psychiatric mood disorders have co-occurring sleep abnormalities, and specifically, problems with REM sleep (Kahn et al., 2013; Palmer & Alfano, 2017; Walker,

2009). Theorists postulate that because of the neuroanatomy, neurophysiology and neurochemical characteristics of REM, it acts as a modulator of emotional brain processes. Empirical studies show that when people are deprived of REM sleep they have intensified experience of negative emotions, show increased anxiety during stressful events, and exhibit less positive reactions to positive events (Mayers & Baldwin, 2006; Walker & van Der Helm, 2009; Zohar et al., 2005). The cyclical nature of this relationship is demonstrated by the fact that pre-sleep mood (particularly a more negative mood state) and contextual situations (particularly stress) shortens REM latency, decreases REM density and duration, decreases dream recall, and disrupts sleep continuity (Buysse, Kupfer, Frank, Monk, & Ritenour, 1992; Cartwright, Luten, Young, Mercer, & Bears, 1998; Cui, Li, Suemaru, & Araki, 2008; Kim & Dimsdale, 2007; Vandekerckhove & Cluydts, 2010; Vandekerckhove et al., 2011).

Sleep and Memory

The ability to effectively remember relies upon the encoding (the transformation of new information into a form that can be stored in memory), consolidation (a largely offline period where new memories become stabilised in the brain) and retrieval of information (Bennion et al., 2015; Payne & Kensinger, 2010). One of the most important ways in which sleep affects cognition is via the role it plays in helping to consolidate memories (Scullin & Bliwise, 2015; Spencer, Walker, & Stickgold, 2017; Stickgold, 2005). The process of *memory consolidation* involves the strengthening of memory traces representing details of our experiences, and the parallel integration of these experiences with previously acquired knowledge (Payne & Kensinger, 2010; Payne & Nadel, 2004). Importantly then, sleep does more than passively protect memories from retroactive interference, but rather actively supports system consolidation of previously acquired information (Diekelmann & Born, 2010; Ellenbogen, Hulbert, Jiang, & Stickgold, 2009; Ellenbogen, Payne, & Stickgold, 2006).

Evidence for sleep-dependent memory consolidation is provided by numerous studies indicating that sleep enhances retention of information learned during waking hours, and that a sleep-filled delay enhances performance on a variety of declarative and non-declarative memory tasks (Dang-Vu, Desseilles, Peigneux, & Maquet, 2006; Diekelmann, Wilhelm, & Born, 2009; Gais & Born, 2004; Marshall & Born, 2007; Nishida, Pearsall, Buckner, & Walker, 2008; Robertson, Pascual-Leone, & Miall, 2004). In contrast, when sleep is disrupted memory performance is poorer than when individuals are allowed to sleep uninterrupted (Ellenbogen et al., 2009; Griessenberger et al., 2012; Wilhelm et al., 2011).

Whereas encoding of environmental events (i.e., acquisition of information) and retrieval of those memories (i.e., reconstruction of previously acquired information) takes place during waking hours, the process of memory consolidation is incompatible with waking consciousness (Diekelmann & Born, 2010). Many studies have shown that after a period of sleep, declarative (Lahl, Wispel, Willigens, & Pietrowsky, 2008; Plihal & Born, 1997; Rasch, Büchel, Gais, & Born, 2007; Tucker et al., 2006), procedural (Fischer, Hallschmid, Elsner, & Born, 2002; Gais, Mölle, Helms, & Born, 2002; Korman et al., 2007; Mednick, Nakayama, & Stickgold, 2003; Stickgold, James, & Hobson, 2000; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000; Walker, Brakefield, Hobson, & Stickgold, 2003), and emotional (Nishida et al., 2008; Payne, Stickgold, Swanberg, & Kensinger, 2008; Wagner, Gais, & Born, 2001) memory recall was superior compared to periods of waking. Hence, when the organism effectively loses consciousness for several hours during sleep, physiological conditions are optimal for memory consolidation to take place. This is why theories regarding the function of sleep have gradually come to accept that a central aspect of that function is to strengthen memories encoded during waking, and transfer their traces into long-term storage (Diekelmann & Born, 2010; Maquet, 2001).

In short, sleep-dependent memory consolidation appears to involve (a) repeated reactivation of information encoded during waking, and (b) transformation of newly-acquired unstable memories into stable representations that become integrated into existing knowledge networks, thus forming long-term memories. In other words, during sleep the organism experiences “off-line” periods (i.e., periods that do not feature the kinds of interference experienced during waking) during which newly-encoded memories are transferred from temporary to long-term stores (Born & Wilhelm, 2012; Walker, 2008). The details of how these steps are accomplished, and which neural regions and neurobiological processes support them, remains somewhat controversial, however (for reviews, see Diekelmann & Born, 2010; Diekelmann et al., 2009; Giuditta, 2014; Stickgold & Walker, 2013; Walker, 2009).

One popular theoretical framework attempting to account for the formation of long-term memory via the consolidation process is a two-stage model that combines the *Active System Consolidation* (ASC) theory (Born & Wilhelm, 2012; see Figure 1.4) and the *synaptic homeostasis hypothesis* (Tononi & Cirelli, 2014). The ASC theory proposes that events experienced during wakefulness that are initially encoded in parallel in hippocampal and neocortical brain regions are then repeatedly reactivated during sleep, and gradually become redistributed so that synaptic connections from the hippocampus to the neocortex are strengthened. These strengthened synaptic connections form persistent and long-term memory traces that are, by and large, stored in neocortical regions (Born & Wilhelm, 2012). This process of reactivation is selective in that not all information learnt during waking is transferred into long-term memory. Instead, information needed to inform future behaviour preferentially encoded, thus ensuring that a system overflow does not occur (Wilhelm et al., 2011).

The ASC theory further proposes that the dialogue between brain systems involved in memory consolidation rely on specific electrophysiological characteristics of NREM sleep (Diekelmann & Born, 2010). These characteristics include the interaction between sleep spindles, hippocampal ripple activity, and slow brain oscillations (Born & Wilhelm, 2012; Ellenbogen et al., 2006; Fogel & Smith, 2011; Stickgold & Walker, 2007). Consistent with this proposal, a plethora of evidence shows that SWS, in particular, provides physiological conditions conducive to this stage of the consolidation process (Diekelmann & Born, 2010; Fogel & Smith, 2011; Gruber et al., 2015; Schabus et al., 2004; Tamminen, Payne, Stickgold, Wamsley, & Gaskell, 2010).

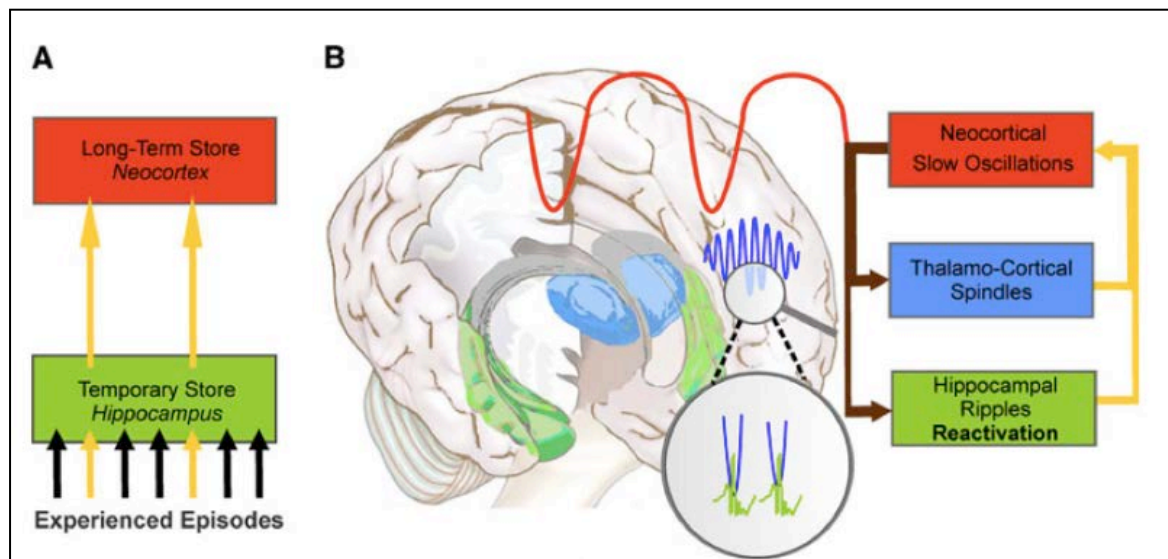


Figure 1.4. The hippocampal-to-neocortical dialogue. **A:** During NREM sleep, memories temporarily stored in the hippocampus are transferred to the long-term store in the neocortex. **B:** The dialogue involves the interaction between the slow oscillations, sleep spindles and hippocampal ripples to create *spindle-ripple events* (magnified circle). From: Born, J., Wilhelm, I. (2012). System consolidation of memory during sleep. *Psychological Research*, 76, 192-203.

The synaptic homeostasis hypothesis proposes that, during waking, learning is accompanied by synaptic potentiation, leading to a net increase in synaptic strength (Dash, Douglas, Vyazovskiy, Cirelli, & Tononi, 2009; Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna, & Tononi, 2008). Then, during sleep, the organism attempts to restore synaptic

homeostasis by reducing synaptic strength. This synaptic down-scaling means there are fewer energy demands on the system, and ensures synapses are refreshed and ready for re-use when further encoding is needed (Dash et al., 2009; Tononi & Cirelli, 2014; Vyazovskiy et al., 2008).

Because REM sleep follows SWS in cyclical fashion during healthy sleep, some researchers have proposed that the particular sequence in which they occur is a key aspect of the memory consolidation process (Giuditta, 2014; Giuditta et al., 1995). This *sequential hypothesis* suggests that SWS supports system consolidation via the reactivation and redistribution of memories to long-term storage, whereas REM sleep supports synaptic consolidation in that it provides ideal physiological conditions allowing additional stabilization of redistributed memory representations that have been transferred to long-term storage (Diekelmann & Born, 2010).

During SWS the slow-oscillations, spindles and ripples co-ordinate the reactivation and redistribution of hippocampal-dependent memories into neocortical sites (Diekelmann & Born, 2010). This reactivation of memory traces leads to reorganisation of the memory representation and changes the quality of the memory, so that implicitly encoded information becomes explicit knowledge. Studies investigating memory tasks that are improved by sleep have found that during SWS, the reactivation of activity patterns evoked during learning positively correlate with memory enhancement the following day (Peigneux et al., 2003; Rasch et al., 2007), and this reactivation seems to occur in cortical neurons during up-states (when neuronal membranes become depolarised and the firing of large groups of neurons occurs) of SWS (Ji & Wilson, 2007). During REM sleep, cholinergic and theta activity allow for synaptic consolidation of the memories already redistributed to the neocortex by facilitating the induction of long-term potentiation (LTP; Huerta & Lisman, 1995; Poe, Nitz, McNaughton, & Barnes, 2000). Furthermore, ponto-geniculo-occipital (PGO) waves during

REM have been associated with learning (Sanford, Silvestri, Ross, & Morrison, 2001). PGO waves occur simultaneously with theta waves during REM, and can lead to the strengthening or weakening of synaptic connections, resulting in efficient network plasticity and the facilitation of LTP (Karashima, Nakamura, Horiuchi, et al., 2002; Karashima, Nakamura, Sato, et al., 2002). The density of PGO waves during REM is positively correlated with post-sleep retention of avoidance learning (Datta, 2000), and the induction of PGO waves, even under conditions of REM sleep deprivation is positively correlated with post-sleep retention of previously-learned information (Datta, Mavanji, Ulloor, & Patterson, 2004).

In summary, then, it appears that NREM and REM sleep play different yet complementary roles in the memory consolidation process. Moreover, not only are specific stages of sleep important for *different aspects of the consolidation process*, they are also important for *consolidation of different types of memory* (Born & Gais, 2003). The dual process hypothesis proposes that hippocampal-dependent declarative memory benefits from early SWS-rich sleep, whereas non-declarative memory (such as procedural, implicit and emotional memory) benefits more from late REM-rich sleep (Gais & Born, 2004). During the night, the brain changes from states that are more conducive to consolidation of episodic memory (i.e., memory associated with a specific spatiotemporal context) to states that are more conducive to consolidation of procedural memories (i.e., a type of implicit memory that involves the unconscious recollection of how to perform a task previously learned via repetition, e.g., riding a bicycle; Payne & Nadel, 2004; Plihal & Born, 1997). Of particular importance to this dissertation is the association between this change of states and HPA-axis action, particularly as the latter relates to cortisol secretion.

Secretory action of the HPA axis is at a minimum during the early part of the night, but reaches a diurnal maximum in the early hours of the morning (Muzur, 2005; Steiger, 2002). Hence, during the early part of the night (i.e., during SWS-rich sleep), lower cortisol

concentrations prevail, and glucocorticoid receptors (GRs) are relatively unoccupied while primary activation occurs among mineralocorticoid receptors (MRs). This physiological state appears to provide optimal conditions for consolidation of hippocampal-dependent episodic memories (Born & Fehm, 1998; Daurat, Terrier, Foret, & Tiberge, 2007; Drosopoulos, Wagner, & Born, 2005; Dudai, Karni, & Born, 2015; Feld & Born, 2017; Payne & Nadel, 2004; Plihal & Born, 1997, 1999; Squire, 1992; Wamsley, Tucker, Payne, Benavides, & Stickgold, 2010). Empirical evidence consistent with this association comes from studies showing that infusion of a low dose of cortisol during early SWS impaired episodic memory recall of word pairs compared to the infusion of a placebo over the same sleep interval, and that administration of the GR agonist dexamethasone during early sleep impaired episodic memory recall of word pairs compared to a placebo condition (Plihal & Born, 1999; Plihal, Pietrowsky, & Born, 1999).

Later in the night and into the early morning (i.e., during REM-rich sleep), cortisol levels are higher and hippocampal functioning is disrupted, leading to interrupted consolidation of episodic memory (Kim & Diamond, 2002; Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Plihal & Born, 1997). However, not all memory consolidation is negatively affected by REM sleep. A series of studies suggest memory for amygdala-dependent emotional material, and for non-hippocampal procedural material, is better consolidated during REM sleep (Born, Rasch, & Gais, 2006; Nishida et al., 2008; Peigneux et al., 2003; Phelps, 2004; Plihal & Born, 1997; Plihal et al., 1999; Stickgold, Hobson, Fosse, & Fosse, 2001; Wagner, Fischer, & Born, 2002; Wagner et al., 2001). For example, Fischer and colleagues (2002) tested motor performance by getting participants to tap a finger sequence as quickly and accurately as possible during two separate conditions. In the first condition, participants were trained on the finger sequencing task at night, followed a period of 8-hours nocturnal sleep, and motor performance was then retested in the morning.

In the other condition, training took place in the morning, followed an 8-hour interval of daytime sleep, and motor performance was then retested in the evening. In both the night-time and daytime retention sleep conditions, improvement in the finger sequence tapping task was proportional to time spent in REM sleep, but did not correlate with time spent in Stage 1, 2 or SWS.

Although the review above implies there is a neat coordination of SWS with consolidation of hippocampal-dependent episodic memories and REM sleep with consolidation of non-hippocampal procedural memories, the literature in this regard is, unfortunately, not quite so unambiguous. For instance, there is evidence that the inhibition of REM sleep does not impair procedural memory for a mirror tracing task (Plihal et al., 1999), or for simple motor tasks (Genzel, Dresler, Wehrle, Grözinger, & Steiger, 2009), and that motor learning and simple motor tasks are in fact, enhanced by the number and density of sleep spindles during Stage 2 sleep and SWS (Fogel & Smith, 2006; Nishida & Walker, 2007; Rasch, Pommer, Diekelmann, & Born, 2009). Consistent with those findings are data from other studies suggesting that SWS and sleep spindles are integral to *both* declarative and procedural memory consolidation (Aeschbach, Cutler, & Ronda, 2008; Gais, Plihal, Wagner, & Born, 2000; Huber et al., 2006; Huber, Ghilardi, Massimini, & Tononi, 2004; Schabus et al., 2004; Schmidt et al., 2006), and other studies reporting that uninterrupted REM sleep improves declarative memory (Fogel, Smith, & Cote, 2007; Rauchs et al., 2004).

Hence, it seems that the literature supports a more nuanced view of the ways in which different stages of sleep support memory consolidation processes (Schabus, 2009). A relatively recent consensus seems to be that the *sequential order* of SWS-REM cycles appears important, with disruptions to this sequence impairing the consolidation process (Ficca & Salzarulo, 2004). In other words, even if a person spends the ‘normal’ amount of

time in SWS and REM, if the cyclical sequence of these sleep stages is disrupted, memory consolidation will not be optimal (Ficca, Lombardo, Rossi, & Salzarulo, 2000).

Sleep is naturally organised as a sequence of NREM-REM cycles, and it is not by coincidence that SWS appears before REM in the sleep cycle. Information acquired during waking is initially processed during SWS, and then during REM sleep in a temporal order (Giuditta et al., 1995). During SWS, non-adaptive memories are weakened and adaptive responses strengthened, and then, during REM sleep adaptive memories are integrated and stored into pre-existing knowledge networks (Ambrosini & Giuditta, 2001; Rasch & Born, 2013; Walker, 2009). Hence, the optimum benefits of sleep on memory consolidation occur when SWS and REM take place in succession. This sequential hypothesis has received support from several human studies. For example, overnight improvement on a visual texture discrimination task was best predicted by the time spent in SWS during the first quarter of the night, and the time in REM sleep during the last quarter of the night (Stickgold, James, et al., 2000). Nap studies have confirmed that when sleep contains both NREM and REM, discriminatory ability on the texture task is superior, compared to sleep containing only early SWS-rich periods or late REM-rich periods (Gais et al., 2000; Mednick et al., 2003).

Several other empirical studies have confirmed that the cyclical nature of NREM-REM throughout sleep plays an important role in memory consolidation. Mazzoni and colleagues (1999; 1994) found that in elderly subjects, the morning recall of words presented before a period of sleep significantly correlated with the time spent in each NREM/REM cycle and the proportion of time spent in each cycle, but not with the absolute amount of time in REM or NREM sleep. Importantly, the disorganisation of sleep cycles was associated with a reduction in morning recall. Indeed, advancing age is associated with reduced sleep continuity and disrupted sleep organization (i.e., a reduction in the number of NREM-REM cycles), which may partially explain the memory deficits often observed in the elderly (Ficca

& Salzarulo, 2004; Mazzoni et al., 1999; Meusel, Grady, Ebert, & Anderson, 2017; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). In another experimental study, participants were subjected to either preserved or disrupted NREM-REM cycles. In these two conditions, the number of sleep cycles differed but the absolute duration of both REM and NREM sleep was the same. Memory retention was superior when sleep was characterised by frequent NREM-REM cycles (as occurs naturally throughout the night) compared to when sleep was characterised by few NREM-REM cycles (Ficca et al., 2000). The above-mentioned studies provide evidence that the cyclical sequence of sleep stages seems important in the memory consolidation process as opposed to the sheer amount of time spent in different stages of sleep.

The literature reviewed above demonstrates that HPA activity (and in particular, the hormone cortisol) plays an important role in sleep regulation and organisation, and that sleep plays an essential role in memory consolidation. While it is clear that sleep and cortisol interact to support memory consolidation, irrespective of sleep, cortisol serves a functional role in memory processes.

Cortisol: A Functional Role in Memory

Cortisol is involved in a wide range of physiological processes, many of which serve to protect the organism. For instance, the hormone plays an important role in lipid and glucose metabolism, maintenance of blood pressure, fluid and electrolyte homeostasis, and protection of the brain against susceptibility to infectious diseases (de Kloet, Oitzl, & Joëls, 1993; Janicki-Deverts, Cohen, Turner, & Doyle, 2016; Reynolds & Walker, 2003; Scheer, Hilton, Mantzoros, & Shea, 2009). Adequate amounts of cortisol are also essential, however, for optimal cognitive functioning (de Kloet et al., 1993; Kirschbaum et al., 1996; Kudielka & Kirschbaum, 2005; Lupien, Gillin, & Hauger, 1999; Wolf, Atsak, De Quervain, Roozendaal, & Wingenfeld, 2016).

The role of cortisol in cognition is enacted via interactions of the hormone with specific brain structures (de Kloet et al., 1993; Kim & Diamond, 2002; McEwen et al., 2015; Schacter & Wagner, 1999; Wingenfeld & Wolf, 2014). The hippocampus (a brain structure vital for memory consolidation and learning; Bird & Burgess, 2008; Davachi & DuBrow, 2015; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Fortin, Agster, & Eichenbaum, 2002; Maguire, Intraub, & Mullally, 2016; Postle, 2016; Tulving & Markowitsch, 1998) and the prefrontal cortex (PFC; a brain structure vital for integrating sensory information, evaluating the meaning of environmental stimuli, and memory processing; Domenech & Koechlin, 2015; Donoso, Collins, & Koechlin, 2014; Euston, Gruber, & McNaughton, 2012; Kane & Engle, 2002; Stokes, 2015) both contain particularly high concentrations of GC receptors (Alderson & Novack, 2002), so that any alterations in cortisol secretion have marked effects on these two brain regions. A robust literature indicates that increased cortisol levels negatively impact performance during the retrieval phase of hippocampal-dependent memory tasks (Atsak et al., 2016; Kirschbaum et al., 1996; Lupien et al., 1997; Lupien et al., 1994; Lupien, Wilkinson, Briere, et al., 2002; Maheu, Collicutt, Kornik, Moszkowski, & Lupien, 2005; Newcomer, Craft, Hershey, Askins, & Bardgett, 1994; Schönfeld, Ackermann, & Schwabe, 2014; Seeman, McEwen, Singer, Albert, & Rowe, 1997; Young, Sahakian, Robbins, & Cowen, 1999), as well as on PFC-dependent working memory and executive functioning tasks (Arnsten, 2009; Arnsten, Raskind, Taylor, & Connor, 2015; Luethi, Meier, & Sandi, 2009; McCormick, Lewis, Somley, & Kahan, 2007; Schoofs, Wolf, & Smeets, 2009).

The most widely accepted taxonomy divides memory into declarative and non-declarative divisions, based on whether task performance relies on the ability to consciously recall information (Schacter & Tulving, 1994). *Declarative memory* refers to memories that are accessible through conscious recollection (Fogel & Smith, 2011). Both *semantic memory*

(general knowledge about events and people, divorced from any spatiotemporal context) and *episodic memory* (memory for events consciously experienced during wakefulness, and with a closely linked spatiotemporal context) are forms of declarative memory (Tulving, 1985; Tulving & Murray, 1985). *Non-declarative memory*, in contrast, does not necessarily require conscious recollection, and hence includes memory performance that is accessible through action, behaviour, and implicit learning (Diekelmann & Born, 2010).

Declarative and non-declarative memory generally rely on different brain structures (Henke, 2010; Reber, Knowlton, & Squire, 1996; Squire, 2004, 2009; Squire & Zola-Morgan, 2015). Declarative memory relies largely on the medial temporal lobe memory system, which includes the hippocampus and adjacent cortical areas (e.g., entorhinal, perirhinal, and parahippocampal cortices; Dudai et al., 2015; Lavenex & Amaral, 2000; Squire & Zola, 1996). Several studies have demonstrated that patients with bilateral damage to the hippocampal formation, particularly the CA1 region, experience severe anterograde amnesia (the inability to form new memories) and temporary retrograde amnesia (the inability to remember previously learned information; Gregory, McCloskey, O'Keefe, & Landau, 2016; Squire, 2009; Squire & Zola, 1996). On the other hand, non-declarative memory relies on more diverse network of brain systems, including but not limited to the striatum, neocortex, amygdala, cerebellum, and the caudate nucleus (Squire, 2004, 2009; Squire & Zola, 1996).

Cortisol, the hippocampus and cognition. GCs (both endogenously secreted and exogenously administered) have particularly dramatic effects on the hippocampus, a brain region critical for new learning, encoding, and retrieval of declarative memories (Davachi & Wagner, 2002; Kim & Diamond, 2002; Reber, Wong, & Buxton, 2002; Squire, 1992, 1993; Squire et al., 1992; Wingenfeld & Wolf, 2014; Wolf, Atsak, Quervain, Roozendaal, & Wingenfeld, 2016). Studies have consistently demonstrated that chronically elevated GCs

impair memory (Belanoff, Kalehzan, Sund, Fleming Ficek, & Schatzberg, 2001; Gold, Drevets, & Charney, 2002; Judd et al., 2014; McEwen & Sapolsky, 1995; Wolf, 2003)⁴.

Structurally and functionally, the hippocampus can be divided into two hemispheres: the right cerebral hippocampus, which is primarily concerned with processing memories of a visual-spatial nature, and the left cerebral hippocampus, which is primarily involved in processing verbal declarative memories (Besson et al., 2014; Frisk & Milner, 1990; Maguire, Burgess, & O'Keefe, 1999; Roche, Mangaoang, Commins, & O'mara, 2005). Elevated cortisol concentrations affect the hippocampus bilaterally, and lead to impaired performance on tests assessing verbal declarative memory and spatial cognition (Baddeley, Kopelman, & Wilson, 2003).

The negative impact of elevated cortisol on verbal declarative memory performance has been demonstrated (a) following increases in endogenous levels of the hormone (e.g., via laboratory-based stress induction procedures; Elzinga & Roelofs, 2005; Kuhlmann, Piel, & Wolf, 2005; Payne et al., 2007; Smeets, 2011; Wolf, Schommer, Hellhammer, McEwen, & Kirschbaum, 2001), and (b) in studies that featured exogenously administered corticosteroids (Buss, Wolf, Witt, & Hellhammer, 2004; Monk & Nelson, 2002; Newcomer et al., 1999; Rimmele, Domes, Mathiak, & Hautzinger, 2003; Tops et al., 2003; Wolf, Convit, et al., 2001). For example, Kirschbaum et al. (1996) found that stress-induced cortisol increases, and (separately) administration of 10 mg hydrocortisone, were associated with poorer recall of previously learned verbal material. Similarly, De Quervain and colleagues (2003; 2000) found that administration of 25mg of cortisone acetate significantly impaired both free and cued recall of verbal material while leaving recognition memory (which is not dependent on

⁴On the other hand, acutely elevated GCs can either enhance (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003; de Kloet, Oitzl, & Joëls, 1999; Lupien & McEwen, 1997; Smeets, Giesbrecht, Jellic, & Merckelbach, 2007; Wolf, 2003) or impair memory depending on several factors, including but not limited to, the time of day of cognitive testing, the stage at which a stressor is applied (i.e., at encoding, consolidation or retrieval), and the dose of GC administered (Het, Ramlow, & Wolf, 2005; Shields, Sazma, McCullough, & Yonelinas, 2017).

hippocampal substrates) unaffected, and that the same dose of cortisone acetate impaired cued recall of word pairs. In their 2003 study, stress-level doses of cortisone acetate reduced cerebral blood flow to the medial temporal lobe (MTL), a memory network that broadly includes the hippocampus.

Several studies have also documented impaired performance on a variety of spatial memory and navigation tasks in the presence of elevated cortisol levels in humans (Duncko, Cornwell, Cui, Merikangas, & Grillon, 2007; Elzinga & Roelofs, 2005; Guenzel, Wolf, & Schwabe, 2014; Kirschbaum et al., 1996; Luine, Villegas, Martinez, & McEwen, 1994; Lupien et al., 1998; Lupien et al., 2005; Schwabe et al., 2007; Taverniers, Van Ruysseveldt, Smeets, & von Grumbkow, 2010; Thomas, Laurance, Nadel, & Jacobs, 2010; but see Driscoll, Hamilton, Yeo, Brooks, & Sutherland, 2005; Klopp, Garcia, Schulman, Ward, & Tartar, 2012; McCormick & Teillon, 2001; Newcomer et al., 1999; van Gerven, Ferguson, & Skelton, 2016). However, investigations of the impact of cortisol on spatial memory are more abundant in the animal literature. Furthermore, studies investigating spatial memory and cortisol in humans have produced more variable results compared to the robust literature on impaired verbal memory in the presence of elevated cortisol levels. Nonetheless, for the most part, literature suggests that hippocampal-based memory is negatively affected by increased cortisol concentrations.

Although hippocampal-dependent forms of memory are impaired by increased cortisol concentrations, non-hippocampal forms of memory, such as procedural memory, appear to be unaffected (e.g., Newcomer et al., 1994; Schwabe et al., 2009; Schwabe & Wolf, 2012). For example, Kirschbaum and colleagues (1996) found that oral administration of 10mg cortisol to healthy subjects impaired performance on a declarative memory but not a procedural memory task. Furthermore, verbal declarative memory is impaired by increasing cortisol levels, whereas non-verbal declarative memory seems to be unaffected (e.g., Lupien

et al., 1997; Lupien, Nair, et al., 1999). For example, Newcomer and colleagues (1999) found that oral administration of cortisol to healthy young adults over a 4-day period impaired their performance on a verbal declarative memory task (a paragraph recall task), but did not significantly affect their performance on a non-verbal memory task (presentation of geometric line drawings and subsequent cued-recall of those images) or on a non-verbal spatial memory task (spatial location task).

Cortisol, the pre-frontal cortex and cognition. Accumulating evidence suggests that acute and chronic elevations of cortisol concentrations can negatively affect the PFC a brain region involved in several cognition domains, including executive functioning, delayed recall of declarative information and working memory⁵ (Arnsten, 2009; Arnsten et al., 2015; Barsegyan, Mackenzie, Kurose, McGaugh, & Roozendaal, 2010; Cornelisse, Joëls, & Smeets, 2011; De Quervain et al., 2000; Elzinga & Roelofs, 2005; Lupien, Gillin, et al., 1999; McCormick et al., 2007; Schoofs et al., 2009; Wolf, Convit, et al., 2001; Wolf, Schommer, et al., 2001; Young et al., 1999; Yuen et al., 2009)

Regarding ways in which the PFC is involved in memory processing, this brain structure plays an important role in the encoding and retrieval of declarative memories (Nyberg et al., 2000), and particularly in post-retrieval monitoring processes. More specifically, during post-retrieval monitoring the PFC is involved in search and decision-making processes necessary to determine whether an event occurred in a specific context (Burgess, 1996; Eichenbaum, 2017), thereby allowing the accurate reconstruction of memories.

Regarding ways in which the PFC is involved in working memory, this brain structure allows us to (a) keep a mental “sketch” of information and protect this information from

⁵WM is generally defined as the temporary storage and manipulation of information (Baddeley, 1992).

internal and external distractions, (b) inhibit inappropriate responses/behaviour, and (c) regulate attention. As such, the PFC allows for cognitive flexibility and goal-directed behaviour (Arnsten, 2009; Arnsten et al., 2015).

Chronically elevated cortisol levels lead to dendritic atrophy in the PFC (Stomby et al., 2016), and strengthens the noradrenalin system which reduces neuronal firing in the PFC (Arnsten et al., 2015; Liston et al., 2006). Stress-induced cortisol release also enhances dopaminergic activity and increases glutamate levels in the PFC (Moghaddam, 2002; Yuen et al., 2009). Glutamate receptor-mediated synaptic transmission in the PFC is particularly important for WM (Goldman-Rakic, 1995; Lisman, Fellous, & Wang, 1998). While acute elevations in glutamate have a positive effect on WM (Yuen et al., 2009), excessive elevations cause impairment. Each of these hormones (noradrenalin, dopamine and glutamate) has an inverted-U influence on WM, with either too little or too much impairing PFC functioning (Arnsten et al., 2015).

Glucocorticoid receptors and memory. Most effects of cortisol on the human brain are mediated by the interaction of GCs with two intracellular receptors (Wolf, 2003). Upon their secretion into the bloodstream, GCs readily enter the brain and alter gene expression by binding to type 1 MRs and type 2 GRs, which bind cortisol with different affinities (de Kloet et al., 1999). MRs have a high affinity for cortisol and become heavily occupied with low cortisol concentrations (including the evening nadir of the cortisol circadian profile, when 90% of MRs but only 10% of GRs are occupied at low cortisol levels). In contrast, GRs have a lower affinity for cortisol and only become heavily occupied when cortisol levels reach a peak (e.g., after a stressor or after the post-awakening cortisol surge; Newcomer et al., 1999; Wingenfeld & Wolf, 2015; Wolf, 2003; Wolf, Atsak, Quervain, et al., 2016).

Although MRs are found predominantly in the hippocampus while GRs are more widely distributed throughout the brain, both play important roles in cognitive function (de

Kloet, 2014; Vogel, Fernández, Joëls, & Schwabe, 2016). MRs are located in brain regions involved in behavioural reactivity to novel situations necessary to encode new information and retrieve it, whereas GRs are located in brain regions involved in the consolidation and storage of learned information (e.g., de Kloet et al., 1998; Judd et al., 2014; Kirschbaum et al., 1996; Roozendaal, 2003), and their relative occupation/non-occupation signal their involvement during these processes. Hence, activation of both types of receptors is a prerequisite for optimal memory functioning. For instance, de Kloet et al. (1999) showed that when cortisol levels were mildly elevated (and therefore all MRs, but only some GRs, were activated), long-term-potential (LTP; the reinforcement of synaptic connections necessary for information storage) was enhanced. However, at higher cortisol levels (when GRs were over-activated and MR occupation was low), LTP was impaired. MRs play a particularly important role in hippocampal-dependent memory, executive function and attention (Cornelisse et al., 2011; de Kloet, 2013; Hinkelmann et al., 2009; Joëls, Karst, DeRijk, & de Kloet, 2008; Otte et al., 2015; Rimmele, Besedovsky, Lange, & Born, 2013). In confirmation of the latter, Schultebras and colleagues (2015) found that verbal memory was significantly better during high MR occupation, and there were trends towards better executive functioning.

Variations in cortisol concentrations and their effects on cognition. As the review above suggests, most studies in this literature have focused on the deleterious effects of *elevated* cortisol levels on cognitive functioning. The negative effects of supra-physiological cortisol levels on brain structure and cognitive functioning have been repeatedly demonstrated in both healthy individuals and in patients known to suffer from chronically elevated cortisol levels (e.g., Cushing's syndrome, depression, Alzheimer's disease; Carpenter & Gruen, 1982; Forget, Lacroix, Somma, & Cohen, 2000; Judd et al., 2014;

Martignoni et al., 1992; Mauri et al., 1993; Mitchell & Denning, 1996; Wingenfeld & Wolf, 2015; Wolkowitz, Reus, Weingartner, Thompson, & Breier, 1990).

Because elevated cortisol levels impair cognitive function due to the effect of the hormone on specific neurobiological systems, it is possible that, for the same reason, low cortisol levels will also have an impairing effect. More specifically, the relationship between cognition and circulating glucocorticoids typically follows an inverted-U shaped pattern (Conrad, Lupien, & McEwen, 1999; Joëls, 2006; McEwen & Magarinos, 1997; McEwen, Nasca, & Gray, 2016), with a certain level of cortisol needed to enhance cognitive functioning (Luine, Martinez, Villegas, Magariños, & McEwen, 1996; Lupien & McEwen, 1997; Lupien, Wilkinson, Briere, et al., 2002), but cortisol levels that are either too low or too high impair cognition (de Kloet et al., 1999; de Kloet et al., 1998; Lupien & McEwen, 1997). In confirmation, Lupien and colleagues (2005; 2002) demonstrated that pharmacological manipulation of GC levels resulting in either too low or too high cortisol levels impaired memory performance.

Given that altered cortisol secretion plays a role in the aetiology of many diseases marked by cognitive impairments (e.g., Addison's disease, Cushing's syndrome, Alzheimer's disease, major depressive disorder, post-traumatic stress disorder, and metabolic syndrome; Belanoff et al., 2001; Hinkelmann et al., 2009; Huang et al., 2009; McNally, 2006; Schultebrasucks et al., 2015; Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2013; Wang et al., 2018; Yates, Sweat, Yau, Turchiano, & Convit, 2012), it is important to determine the physiological mechanisms by which chronically altered circadian and ultradian rhythms impact cognitive functioning. One such mechanism may be through sleep, given that a bidirectional relationship exists between circadian rhythmicity and the sleep-wake cycle, and because successful memory consolidation of information learned during the day is known to rely on sleep.

Addison's Disease

First described by Thomas Addison in 1855, and hence commonly referred to as Addison's disease, the endocrinological disorder of primary adrenal insufficiency (AI) is potentially life-threatening if left untreated. Primary AI results from pathological destruction of the adrenal cortex (by, for example, autoimmune antibodies or haemorrhage), with consequent hypocortisolaemia (i.e., decreased production of glucocorticoids and mineralocorticoids; Løvås & Husebye, 2003). A secondary form of hypocortisolaemia results from disruption of the HPA axis by, for example, hypothalamic-pituitary tumours that cause inadequate release of ACTH, and hence a lack of sufficient stimulation for the adrenal glands to produce cortisol (Elder & Dimitri, 2015). Another important cause of hypocortisolaemia is the suppression of HPA-axis activity by exogenous GC treatment such as oral GC steroids, GC-based inhalers (typically used by asthma patients) or GC-based creams (typically used by eczema and dermatological patients; Arlt, 2009).

Diagnosis of AD is therefore based on the measured presence of low plasma cortisol, low aldosterone levels, high renin levels, and elevated ACTH (loss of endogenous ACTH drive; Anglin, Rosebush, & Mazurek, 2006). Because the disease often presents insidiously, it is frequently unrecognised in its early stages (Ten, New, & Maclaren, 2001). This is extremely problematic because delayed diagnosis can result in death (Oelkers, 1996). Patients with AD can have decreased longevity due to stress-induced crises (Arlt & Allolio, 2003), or to an adrenal crisis that results in patients collapsing and going into a coma due to hypotension and hypoglycaemia (Elder & Dimitri, 2015). They are also predisposed to cardiovascular disease, and are at high risk of developing infections.

Epidemiology and etiology. AD is relatively uncommon, with an estimated global prevalence ranging from 39-144 per million and an incidence rate of 4-6 per million per annum (Bergthorsdottir, Leonsson-Zachrisson, Odén, & Johannsson, 2006; Kong &

Jeffcoate, 1994; Løvås & Husebye, 2002; Ten et al., 2001). In South Africa the prevalence is lower, at 3.1 per million utilising a case finding study (Ross & Levitt, 2013). The disease is more common in women, and is most frequently diagnosed between the ages of 30 and 60 years (Kong & Jeffcoate, 1994; Oelkers, 1996).

Regarding etiology, tuberculosis adrenalitis was once considered the most common cause of AD, and is still a serious cause in low- and middle-income countries. More recent studies suggest, however, that autoimmune adrenalitis is the most common cause, accounting for 80-90% of adult AI cases (Arlt & Allolio, 2003). Infections (tuberculosis, HIV, and syphilis), metastatic disease, drugs, and adrenoleukodystrophy are also common aetiological factors (Anglin et al., 2006). In South Africa, as in most industrialized countries of the global north, the predominant underlying etiology is autoimmune related (Ross et al., 2010).

Treatment. Patients with AD need to be on lifelong glucocorticoid replacement therapy. Such treatment is essential for survival (Arlt & Allolio, 2003). Cortisol is normally replaced with oral hydrocortisone, prednisone or cortisone acetate (all of which activate predominantly GRs, predominantly), plus an additional mineralocorticoid (fludrocortisone) to control sodium and potassium balance (Ten et al., 2001; Tytherleigh, Vedhara, & Lightman, 2004).

Typically, GCs are replaced in 2-3 daily doses, with the total dose ranging from 15-30mg. The highest dose (one-half to two-thirds) is taken in the morning, a reduced dose is taken in the afternoon, and (if required) a third dose in the late afternoon/evening (typically around 5pm; Johannsson et al., 2015; Peacey et al., 1997; Suliman et al., 2003). For example, Arlt (2009) recommends a total daily dose of 20mg, split up as follows: 15mg in the morning and 5mg 6 hours later, or 10mg in the morning, 5mg 4 hours later, and a further 5mg 8 hours later.

Such a dosing schedule of GC replacement is meant to imitate the normal diurnal cortisol rhythm, to reflect the peak rise in cortisol in the morning, and to avoid over replacement during the night-time nadir of physiological cortisol secretion (Johannsson et al., 2015; Mah et al., 2004). However, despite efforts to find the best replacement regimen in terms of dosage and timing (Groves, Toms, Houghton, & Monson, 1988; Howlett, 1997; Mah et al., 2004), none mimic the physiological circadian rhythm; there are still supra-physiological peaks during the day and lower-than expected concentrations during the early hours of the morning (Blomgren, Ekman, Andersson, & Arnqvist, 2004; Chan & Debono, 2010; M Debono, Ross, & Newell-Price, 2009; Derendorf et al., 1991; Johannsson et al., 2012; Simon et al., 2010). Another problem with GC replacement therapy is that it does not properly mimic the early morning rise in cortisol levels experienced by healthy individuals. In healthy individuals, the natural peak of cortisol starts during the onset of REM sleep in the early hours of the morning, whereas the peak level resulting from an early morning dose of hydrocortisone comes several hours after the medication has been taken (Ten et al., 2001). This temporary early-morning cortisol insufficiency in patients with AD can account for commonly reported symptoms such as fatigue, nausea, and headaches, which are alleviated within an hour after taking the morning dose of hydrocortisone (Clow, Thorn, Evans, & Hucklebridge, 2004).

Further regarding dosage, body weight is an important factor to consider, with the common recommendation being a weight-adjusted hydrocortisone dose of 0.12 mg/kg of body weight (M Debono, Ross, et al., 2009). During times of stress (e.g., high temperature, surgery, and trauma), the recommendation is that GC doses are doubled or even tripled to help the body cope (Elder & Dimitri, 2015; Falorni, Minarelli, & Morelli, 2013).

Mineralocorticoid depletion is treated with fludrocortisone at a dose of 0.05-0.2 mg/day (Arlt et al., 1998), typically taken in the morning. Fludrocortisone doses may need to

be adjusted if blood pressure or sodium and potassium levels are elevated or suppressed, and during pregnancy when increased progesterone levels exert anti-mineralocorticoid activity (Arlt, 2009).

An important point to make here is that although replacement therapy replenishes adrenal hormones, it does not restore the normal circadian rhythm of hormone release (Arlt, Rosenthal, Hahner, & Allolio, 2006; Chan & Debono, 2010). Instead, patients are over-replaced immediately following therapeutic administration, and then under-replaced within a few hours of that administration (Løvås & Husebye, 2007; Mah et al., 2004). This over- and under-replacement results from the biochemical properties of replacement medications. Oral HC is absorbed rapidly, achieving maximal plasma concentrations an hour after intake (Elder & Dimitri, 2015). However, HC replacement produces extremely variable peak concentrations within a supra-physiological range, followed by rapid declines to $<100\text{nmol/l}$ at 5-7 hours after ingestion (Arlt, 2009) due to its short plasma half-life (around 1.5-1.8 hours; Chan & Debono, 2010; Lennernäs, Skrtic, & Johannsson, 2008). This means that patients require regular dosing, and that they nonetheless experience periods of cortisol deficiency, particularly between midnight and the early hours of the morning (Harbeck, Kropp, & Mönig, 2009). Given the overall tenor of the literature reviewed earlier, this latter fact may have important implications for sleep regulation.

Patients with AD also have an ACTH profile opposite to that of cortisol, with high concentrations before their morning dose and rapidly declining concentrations (accompanied by increasing cortisol levels) after GC ingestion (Arlt et al., 2006; Ekman et al., 2012; Feek et al., 1981; Scott, Donald, & Espiner, 1978). Patients experience difficulties in suppression of nocturnal ACTH secretion. The early morning adrenal insufficiency that typically occurs when the traditional regimen is administered results in plasma ACTH concentrations that are much higher than normal for several hours in the early morning (Feek et al., 1981; Ten et al.,

2001). Furthermore, because ACTH secretion may become inadequately inhibited on a chronic basis in these patients, it may eventually become poorly suppressible.

While no conventional replacement regimen replicates the natural circadian rhythm except that of newer dual release hydrocortisone (plenadren®, discussed below), patients on a 3-daily regimen have shown more constant cortisol levels (Groves et al., 1988; Howlett, 1997; Mah et al., 2004) compared to patients on 1- or 2-daily regimens (see Figure 1.5), who typically experience cortisol deficiencies by the late afternoon (by 4pm; Groves et al., 1988).

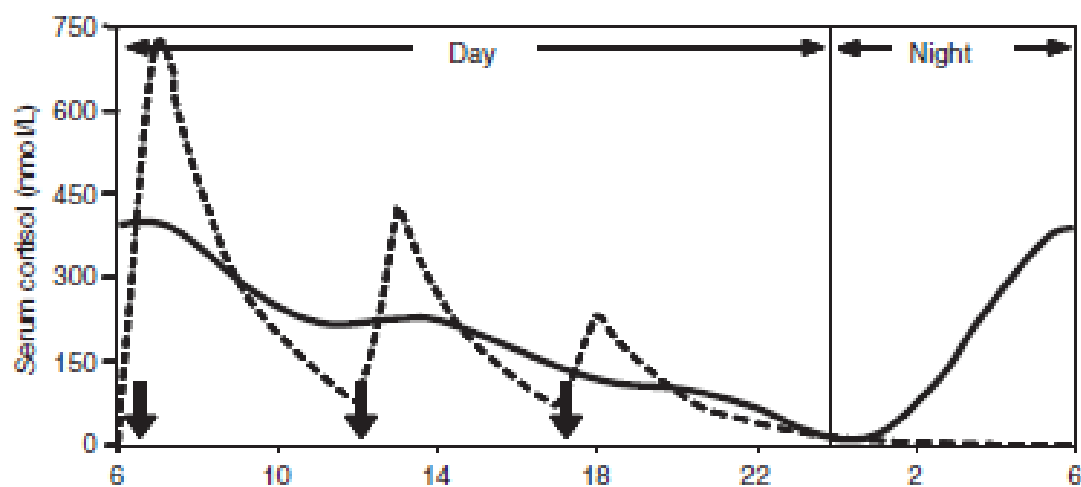


Figure 1.5. Simulated cortisol profile for a patient [broken line] following thrice-daily hydrocortisone administration [10mg at 06:00, 5mg at 12:00 and 2.5mg at 18:00, shown as solid arrows]. The normal circadian rhythm of cortisol [solid line]. From: Mah, P. M., Jenkins, R. C., Rostami-Hodjegan, A., Newell-Price, J., Doane, A., Ibbotson, V., ... & Ross, R. J. (2004). Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. *Clinical endocrinology*, 61(3), 367-375.

New advancements in treatment. Because standard replacement therapy does not mimic the natural circadian rhythm, newer treatments aim to imitate physiological cortisol rhythms. These new treatments are attempting to improve biochemical control of the secretion of cortisol, and reduce long-term adverse effects, as are typically associated with standard replacement regimens (Elder & Dimitri, 2015). Continuous subcutaneous HC

infusion (CSHI) and modified release HC (MR-HC) tablets are two promising new treatments.

Infusion of HC in patients with AD has been shown to mimic normal circadian rhythmicity and improve QoL (Løvås & Husebye, 2007; Merza et al., 2006). A crossover randomised clinical trial ($N = 33$ patients with AD who received CSHI or thrice-daily conventional therapy for a 3-month period), found that a 10mg/m^2 daily dose of CSHI normalised cortisol and ACTH levels in the morning, and that 24-hour cortisol curves resembled normal circadian variation compared with conventional oral replacement. The 24-hour area under the curve (AUC) did not differ between infusion and conventional oral therapy, but daytime AUC (8am-midnight) was higher for oral replacement therapy, and night-time AUC (midnight-8am) was higher for CSHI. Infusion improved vitality and physical functioning (Øksnes et al., 2014), but did not improve sleep (except that sleep length increased, as measured by the Pittsburgh Sleep Quality Index (PSQI) and actigraphy). Therefore, despite mimicking the physiology of endogenous cortisol secretion, sleep was not improved. However, measurement via self-report and actigraphy provides less robust data than polysomnographic measurements, and do not generate measurements of sleep architecture. Furthermore, previous studies have shown a discrepancy between self-report, actigraphy based measurements, and polysomnographic measurements of sleep (Armitage, Trivedi, Hoffmann, & Rush, 1997; Bathgate, Edinger, Wyatt, & Krystal, 2016; Løvås, Husebye, Holsten, & Bjorvatn, 2003; Matthews et al., 2018; O'Hare et al., 2015). Another randomised double-blind placebo-controlled clinical trial ($N = 10$ patients with AD) assessed whether CSHI improved QoL and fatigue compared to standard GC therapy (Gagliardi et al., 2014). CSHI did not improve health status in AD patients who had mild deficits in well-being at baseline. Overall, then, it appears that CSHI benefits some, but not all, patients in that it

restores the usual circadian cortisol rhythmicity and improves QoL (Løvås & Husebye, 2007).

A significant disadvantage of subcutaneous infusions is their impracticality. An alternative is for patients using IR-HC to wake up at 3am and take a dose of medication, is perhaps even more impractical, and, moreover, may cause more daytime fatigue as well as supra-physiological peaks. Modified release HC (MR-HC) offers a more practical and sustainable approach to normalising cortisol circadian rhythms due to its immediate and extended hormone release characteristics.

MR-HC has been shown to mimic natural physiological cortisol circadian rhythm (M Debono, Ghobadi, et al., 2009; Johannsson et al., 2009). Johannsson and colleagues (2009) demonstrated that taking a once off morning dose of either 5 or 20mg MR-HC led to a close mimicking of physiological cortisol circadian rhythms, except for the early-morning cortisol peak. However, if MR-HC is taken late at night (thus allowing for a delayed and sustained release), it can mimic the rise in cortisol that typically occurs during the early hours of the morning. For example, Debono et al. (2009) showed that taking 15-20mg of MR-HC at 23h00 and 10mg at 07h00 reproduced the normal physiological cortisol circadian rhythm in healthy controls (see Figure 1.6). In that study, participants' cortisol levels peaked, on average, at 08h32 and decreased throughout the day, reaching a nadir, on average, at 00h18. MR-HC therefore offers a more effective treatment that could reduce morbidity and mortality rates and improve quality of life in patients with AD (Chan & Debono, 2010).

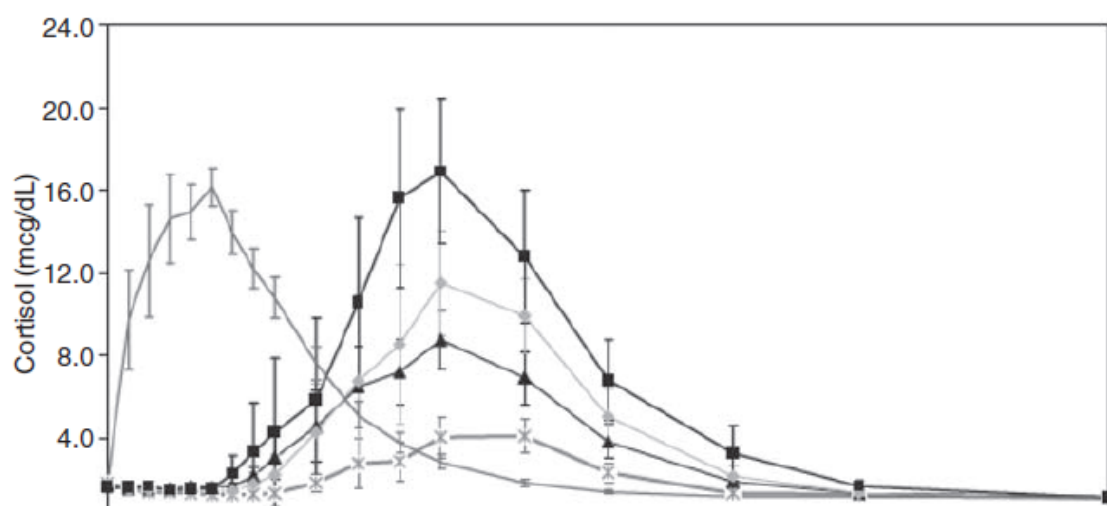


Figure 1.6. Concentration-time profiles for modified-release hydrocortisone (MR-HC) 5mg, 10mg, 15mg and 30mg compared with immediate-release hydrocortisone (IRHC). Graph showing delayed and sustained release characteristic of MR-HC (to convert values from mcg/dl to nmol/l x 27.59). From: Debono, M., Ghobadi, C., Rostami-Hodjegan, A., Huatan, H., Campbell, M. J., Newell-Price, J., ... & Ross, R. J. (2009). Modified-release hydrocortisone to provide circadian cortisol profiles. *The Journal of Clinical Endocrinology & Metabolism*, 94(5), 1548-1554.

Subjective health status and quality of life in AD. Although the term “quality of life” (QoL) is used frequently in colloquial language and is generally understood by laypeople, in psychology and the health sciences it has proven a difficult-to-define construct, with no universal agreement on its constitution (Diener & Suh, 1997; Kind, Hsu, Wang, Yao, & Tang, 2003; Saxena, Carlson, Billington, & Orley, 2001; The WHOQOL Group, 1998). There is some consensus, however, around the fact that QoL is a multidimensional concept. For instance, the World Health Organisation (WHO) suggests QoL must be broadly defined as including physical, psychological, and social dimensions, and that the construct refers specifically to “individuals’ perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (The WHOQOL Group, 1998, p. 11).

Previously published studies focused on QoL in patients with AD have consistently shown that, despite being on replacement therapy, these individuals still report reduced QoL, with predominant complaints including increased fatigue, lack of energy, depression and anxiety, as well as reduced stress tolerance and reduced ability to cope with daily demands (Arlt & Allolio, 2003; Hahner et al., 2007; Løvås & Husebye, 2003; Løvås, Loge, &

Husebye, 2002; Thomsen, Kvist, Andersen, & Kessing, 2006). A worldwide survey of 1245 patients with AI (84% of whom had AD) found that, despite being on replacement medication, 64% reported reduced subjective health status, 40% reported regular absence from work/school, 76% were concerned about the long-term side-effects of replacement medication, and 38% had been hospitalised in the year prior to reporting (Forss, Batcheller, Skrtic, & Johannsson, 2012). Regarding affective disorders, a Danish study of 989 patients with AD found they were 2.68 times more likely to suffer from depression than a control group with osteoarthritis (Thomsen et al., 2006). Studies have also found that the rate of unemployment, and proportion of individuals receiving disability benefits, is higher in patients with AD than in the general population (Hahner et al., 2007; Løvås et al., 2002). Cumulatively, there is increasing evidence that replacement therapy fails to restore subjective health in AD patients, possibly due to the inability of standard GC replacement to mimic circadian variation in cortisol (Hahner et al., 2007; Løvås et al., 2002).

Despite the problems with replacement regimens, replacing GC's in the appropriate quantities is essential for improving QoL. Inadequate GC replacement can lead to chronic fatigue, malaise, diarrhoea, abdominal pain, weight loss, poor stress and immune responses, electrolyte abnormalities and nocturnal hypoglycemia. On the other hand, excessive replacement can lead to glucose intolerance, hypertension, cardiovascular disease, raised intraocular pressure, psychiatric illness (e.g., manic and/or depressive episodes), osteoporosis, gastric ulcers, poor wound healing, protein catabolism, and life-threatening adrenal crisis (Arlt & Allolio, 2003; Arlt et al., 2006; Ten et al., 2001). In addition, high doses of HC may also disrupt sleep, which is postulated to be a cause of the fatigue often experienced by patients (Løvås et al., 2003; Løvås et al., 2002).

Fatigue is a specific feature of adrenal failure that is of particular import in the current dissertation. Numerous studies suggest that, in patients with AD, clinically relevant fatigue

persists despite replacement therapy. For instance, Løvås, Loget, and Husebye (2002) found that patients with AD self-reported reduced general health perception and vitality despite receiving replacement therapy with cortisone acetate and fludrocortisone. Similarly, van der Valk and colleagues (2016) found that 48% of their patient sample ($N = 328$) reported abnormal fatigue and 61% reported severe fatigue.

Researchers postulate that these reports of increased daytime fatigue may be due to reduced quality of sleep in patients with AD, and that, in turn, high doses of HC may contribute to those sleep disruptions (García-Borreguero et al., 2000; Løvås et al., 2002). For instance, Løvås, Husebye, Holsten, and Bjorvatn (2003) found that 34% of the patients with AD in their sample ($N = 60$) reported weekly sleep disturbances (difficulties falling asleep (13%), repeated awakenings (14%), and early morning awakenings (20%)).

Because disrupted circadian rhythms are related to metabolic abnormalities, poor QoL and fatigue, and given the bidirectional relationship between cortisol and the sleep-wake cycle, the dosage, timing and type of medication regimens used by patients may impact their general well-being and sleep patterns (Buckley & Schatzberg, 2005) due to GCs influence on circadian rhythmicity.

QoL and medication regimens. Several studies have found that patients who take higher doses of HC experience more impaired QoL. For instance, those taking doses greater than 25mg per day have worse QoL compared to patients taking lower doses (Ragnarsson et al., 2014). Bleicken and colleagues (2010) found, in their cross-sectional study of 194 primary adrenal insufficiency (PAI) and 140 secondary adrenal insufficiency (SAI) patients, that patients on HC doses greater than 30mg scored significantly lower on two of the short-form-36 (SF-36) subscales (specifically, general health perception and role functioning-physical) compared to patients on lower doses. Similarly, Tiemensma and colleagues (2014)

found that patients with PAI on higher doses were more depressed, and experienced more QoL impairments, than matched healthy controls.

Although several studies (e.g., Alonso et al., 2004; Behan et al., 2011; Bleicken et al., 2008; Ekman et al., 2012; Wichers, Springer, Bidlingmaier, & Klingmüller, 1999) suggest that the actual number of doses administered has no effect on health-related QoL, numerous others have found significant effects of number of doses on QoL. Within this latter group of studies, however, the direction of that influence remains contested. For instance, whereas Groves et al. (1988) suggest that a three times daily intake improves QoL more than a two times daily intake, other studies suggest the direct opposite (Benson et al., 2012; Bleicken et al., 2010; van der Valk et al., 2016). Consistent with the latter group of studies, Riedel et al. (1993) and Wichers et al. (1999) found that a twice-daily dosage improved QoL compared to a once-daily dosage. Of note, however, is that none of these studies found that replacement therapy improved QoL scores to the same level as the general population.

In terms of the effects of type of replacement medication, QoL is reduced in patients with AD irrespective of type of GC replacement (hydrocortisone, prednisone, and cortisone acetate; Bleicken et al., 2008; Løvås et al., 2002), supporting the notion that replacement therapy fails to normalise QoL.

Cognitive functioning in patients with AD. Patients with AD, even those on replacement therapy, frequently present with both subjective cognitive complaints and objective cognitive impairments. For example, Klement et al. (2010) reported that patients with AD on replacement therapy performed significantly more poorly than healthy controls on a declarative memory test. On average, AD patients recalled 8.7 words from a 30-item list, whereas healthy controls recalled 10.4 words. Similarly, Schultebrasucks and colleagues (2015) found that patient performed significantly more poorly than controls on a test of verbal learning, and Tiemensma and colleagues (2016) found that patients with AD

performed significantly more poorly on tests of both verbal and visual memory than healthy controls. The latter study also found mild executive impairment and significantly slower processing speed in their patient group. Interestingly, in that study delaying HC intake in another group of patients with AD (which resulted in significantly lower cortisol levels at time of cognitive testing) had no negative impact on cognitive performance.

Overall, it appears that cognitive deficits in patients with AD are primarily in the domain of declarative memory (both verbal and visual memory), but also extend to executive functioning and processing speed.

One neurobiological mechanism that may account for these memory impairments are the sub- or supra-physiological cortisol levels that patients experience regularly. These profound GC fluctuations may result in neuronal death or malfunction in the hippocampus and the PFC, which may explain a cognitive profile that features prominent deficits in declarative memory and executive functioning. In support of this conjecture, elevated cortisol levels associated with normal aging have been linked to ventricular enlargement, neuronal loss or malfunction, and decreased hippocampal volume (De Leon et al., 1997; Geerlings et al., 2015; Lupien et al., 1998; Sapolsky et al., 1986; Travis et al., 2016). Furthermore, exogenous administration of hydrocortisone to healthy subjects (resulting in elevated cortisol levels) impairs verbal memory, working memory, visuo-spatial memory, and executive functioning (De Quervain et al., 2000; Fleischer et al., 2018; Lupien, Gillin, et al., 1999; Newcomer et al., 1999; O'Brien, Schweitzer, Ames, Tuckwell, & Mastwyk, 1994; Wolkowitz et al., 1990). Similarly, exogenous administration of dexamethasone or prednisone to healthy subjects impairs memory performance (Newcomer et al., 1994; O'Brien et al., 1994; Schmidt, Fox, Goldberg, Smith, & Schulkin, 1999; Wolkowitz et al., 1990).

Another neurobiological mechanism (related to the latter mechanism discussed above) that might explain the memory deficits observed in patients with AD is differential activation

of the two types of glucocorticoid receptors discussed earlier, MRs and GRs. Activation of MRs is essential for successful encoding, whereas activation of GRs (in addition to the already activated MRs) is essential for successful consolidation and retrieval (de Kloet et al., 1999; Kirschbaum et al., 1996). A balanced activation of both receptors may be needed for optimal memory functioning in humans. In one study providing empirical support for this proposed neurobiological mechanism, Tytherleigh et al. (2004) found that adequately treated AD patients performed significantly better on the recall phase of a declarative memory recall task when both receptor types were activated compared to when only one or the other was activated. Empirical studies suggest that some cortisol is needed to enhance cognition (a shift towards predominant MR activation and minimal GR activation), but that prolonged exposure/high concentrations of cortisol (predominant GR activation) have impairing effects (de Kloet et al., 1999; Groch, Wilhelm, Lange, & Born, 2013; Hinkelmann et al., 2015; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007; Lupien, Wilkinson, Brière, et al., 2002). In support of the beneficial effects of MRs on cognition, Schultebrasucks et al. (2015) used a repeated-measures crossover design and either administered patients with AD fludrocortisone (resulting in high MR occupation) or withheld the same drug from them (resulting in low MR occupation). Verbal memory performance was significantly better in the condition that featured high MR occupation, and there also were trends towards better executive functioning in the condition. However, conventional replacement used by patients with AD leads to periods of sub- and supra-physiological cortisol concentrations, which may result in under activation of MRs and overactivation of GRs respectively, and subsequently have a negative impact on cognitive functioning in these patients.

Overall then, although studies report that patients with AD frequently complain of memory problems, very few have explored, using detailed objective measures, the characteristics of these memory deficits (e.g., how severe they are relative to normal

performance, and whether forms of non-declarative memory are affected as much as declarative forms are).

Sleep disruption in patients with AD. As noted earlier, patients with AD report increased daytime fatigue, which may be due (at least partially) to the reduced quality of sleep they report and experience. In terms of subjective sleep quality, Løvås and colleagues (2003) found that patients self-reported difficulties falling asleep, repeated night-time awakenings, and early morning awakenings. In terms of objectively measured sleep quality, García-Borreguero and colleagues (2000) found that patients who took a dose of hydrocortisone before bedtime had significantly reduced wake after sleep onset (WASO), reduced REM latency, and increased REM sleep time compared to those whose hydrocortisone medication had been withheld for 1.5 days. There were no observed between-group differences in terms of NREM sleep parameters, or other sleep parameters such as sleep efficiency and latency, however.

Limited knowledge exists on the impact of low cortisol on sleep architecture and similarly, few studies on sleep of patients with AD when replacement medication is administered as per normal. Only one study, more than 25 years ago reports on both these situations (Gillin, Jacobs, Snyder, & Henkin, 1974b). They reported that when medication was administered as per normal, patients with AD had similar sleep to controls, except that patients took significantly longer to fall asleep and spent significantly more time in Delta sleep. They also found that patients with AD whose replacement medication was withheld for more than 24 hours (and who therefore had undetectably low levels of cortisol at bedtime) showed increased time spent in SWS and corresponding reduced time spent in REM sleep. Similarly, García-Borreguero et al. (2000) reported that patients with AD who were deprived of glucocorticoid medication for 1.5 hours prior to bedtime (and who therefore had undetectably low levels of cortisol at bedtime) showed increased REM latency and decreased

amount of time spent in REM sleep compared to patients who took their medication just before bedtime. These results suggest that cortisol is needed to facilitate the initiation and maintenance of REM sleep. In contrast, high cortisol concentrations appear to reduce the amount of time spent in SWS (Bliwise, 1993; Born et al., 1989; Steiger, 2003), and, consistent with this, decreased concentrations of cortisol in healthy controls and patients with AD is significantly associated with increased delta sleep (Gillin et al., 1974b).

Overall then, few studies have objectively assessed sleep in patients with AD, despite that fact that an abundance of scientific evidence suggests disruptions to cortisol's circadian rhythm have negative effects on sleep architecture. For instance, patients with psychiatric conditions that feature elevated cortisol levels (e.g., depression and PTSD) experience less time in SWS, shortened REM latency, increased REM sleep and density, and sleep discontinuity (Armitage, 2007; Armitage et al., 2001; García-Borreguero et al., 2000; Koffel, Khawaja, & Germain, 2016; Shipley, Schteingart, Tandon, & Starkman, 1992; Tsuno, Besset, & Ritchie, 2005). Similar patterns of decreased REM latency and/or increased time spent in REM sleep have been found in patients with AD who took hydrocortisone before bedtime and in healthy controls with artificially increased cortisol levels (García-Borreguero et al., 2000; Vgontzas et al., 1997). There is comparatively little literature on sub-physiological cortisol levels and sleep, and similarly, few studies on sleep of patients with AD when replacement medication is administered as per normal. Therefore, effects on sleep quality and architecture of the illness itself, and of replacement therapy, remains largely unexplored in patients with AD.

Given the importance of the HPA axis in sleep regulation (Born et al., 1989; Buckley & Schatzberg, 2005), either low or high night-time cortisol, alongside high night-time ACTH and CRH may lead to sleep disturbances in patients with AD (Øksnes et al., 2014). However, the implications of exposure to altered circadian cortisol patterns and consequent sleep

disruptions have not been adequately addressed in the existing literature. For instance, disrupted sleep may impede sleep-dependent memory consolidation. Since changes in sleep and memory are associated with the use of corticosteroids, further research is necessary to help understand the impact that replacement medication used by patients with AD has on the processes that influence sleep-dependent memory consolidation.

Overall Aims and Rationale

A strong line of research indicates that healthy sleep plays a significant role in memory consolidation, and that alterations in cortisol activity have negative effects on sleep architecture and, via that mechanism, on memory performance. Sub- and supra-physiological cortisol levels resulting from conventional replacement therapy are suspected to be a major cause of reduced QoL, sleep disturbances, and cognitive impairment in patients with AD. As such, this population provides a unique opportunity to study the effect of altered cortisol concentrations on sleep and sleep-dependent memory consolidation.

The novelty of the research program described in this dissertation is that it investigates the relationship between altered nocturnal circadian rhythms, sleep architecture, and cognitive functioning in patients with AD. Although previous research suggests that both cognitive and sleep complaints are (a) frequently reported by these patients, and (b) affected by altered cortisol levels, only a few have used objective measures to measure either sleep patterns or memory impairments experienced by patients with AD. Prior to the current investigations, no published study had undertaken to investigate, in patients with AD, (a) associations between sleep disruptions and memory impairments, (b) the various types of memory systems and processes that might be affected, or (c) how these memory deficits relate to altered circadian rhythms and consequent sleep disruptions. With specific regard to patients with AD, investigating relations between sub- and supra-physiological cortisol levels, sleep architecture, and cognition may help understand how, for instance, conventional replacement therapy might contribute to reduced quality of life. This information would provide the first step in understanding how modifying medication regimens could improve patients' lives, an understanding that is especially important because cortisol replacement therapy is required lifelong. From a broader neuroscientific perspective, patients with AD provide a unique opportunity to simultaneously study the effects of hyper- and hypo-

cortisolism on sleep quality, memory performance, and sleep-dependent memory consolidation. Careful study of these patients can help unravel the distinct roles that sub- and supra-physiological GC levels play in sleep regulation/structure and in sleep-dependent memory consolidation.

Summary:

Descriptions, aims/objectives, and hypotheses of Study 1 – Study 4

Study 1: Self-reported Quality of Life, Sleep Quality, and Cognition in Patients with Addison's disease

This study used survey methodology to enquire about a range of physical and psychological symptoms of South African patients with AD, with a particular focus on subjective health status and overall QoL, symptoms of affective psychiatric disorders (depression and anxiety), sleep quality, and cognition.

Specifically, the study investigated whether, relative to matched healthy controls, patients who are adequately replaced with hydrocortisone and a mineralocorticoid have impaired subjective health perception and QoL, increased fatigue (both mental and physical), reduced vitality, increased anxiety and depression, increased subjective sleep disturbances, and impaired cognition (memory and attention deficits). The focus was on these particular physical, affective, and cognitive outcomes because previous studies, using samples of patients with AD from Europe and North America who were on standard replacement therapy, suggest deficits in these areas frequently emerge in such patients. Furthermore, the study sought to describe associations between physical, affective, and cognitive variables and overall QoL (e.g., to assess whether there are significant relations between sleep quality and cognition, and whether poor sleep quality is a significant predictor of impaired QoL).

Study 2: Cognitive Function in Patients with Addison's disease

This study used objective measures of cognition to compare performance of patients with AD to that of matched healthy controls in the domains of executive function, reasoning, episodic memory, working memory and attention, and processing speed. The novelty of this study is that it used a telephonic cognitive assessment tool, and that it tested the specific prediction (based on theory, as well as on findings from the few previous studies in this area) that patients will have significantly impaired episodic memory but relatively intact performance in other cognitive domains.

Study 3: Associations between Sleep Quality and Cognitive Function in Patients with Addison's disease

This study used objective measures of sleep architecture and of memory performance to investigate whether sleep augments memory consolidation in patients with AD as it does in healthy controls. Two groups of participants (patients with AD, who are known to have altered circadian rhythms which may influence sleep, and matched healthy controls, who presumably have a normal diurnal cortisol rhythm) were assessed under two conditions: *Sleep* (an 8-hour period of sleep separated learning of declarative information from a recall test of that information) and *Wake* (an 8-hour period of normal waking activity separated learning of declarative information from a recall test of that information).

The rationale for this investigation emerges from the literature review above. In short, numerous studies indicate that healthy sleep benefits memory consolidation, and that sleep disruptions (e.g., as might be present in individuals with abnormal night-time cortisol concentrations) might impede the beneficial effects of sleep on memory consolidation. Hence, the study tested the specific hypotheses that (a) compared to matched healthy controls, patients with AD will have poorer sleep quality (as measured by actigraphy) and will perform more poorly on standard memory tests, (b) both patients and controls will have

better memory performance in the *Sleep* than in the *Wake* condition, and (c) a period of sleep will be significantly more beneficial for memory consolidation in healthy controls than in patients.

Study 4: Associations between Sleep Quality and Night-time Cortisol Concentrations in Patients with Addison's disease

Results of Study 2 and Study 3 indicated that patients with AD have objectively measured deficits in the domain of episodic memory, and that sleep-dependent memory consolidation processes do not operate as efficiently in patients as in matched healthy controls. Because previous literature suggests that disrupted circadian rhythms have negative effects on sleep architecture and sleep-dependent memory consolidation processes, the final study presented within the current dissertation investigated whether alterations in cortisol's circadian rhythms are associated with altered sleep architecture in patients with AD. The study tested the specific hypothesis that compared to matched healthy controls, patients with AD, possibly due to their alternating periods of sub- and supra-physiological cortisol concentrations, will experience (a) poorer sleep quality, (b) disrupted sleep architecture, and (c) higher cortisol concentrations during the first half of the night, but lower concentrations during the second. Finally, we explored associations between cortisol concentrations and sleep patterns.

CHAPTER THREE:

STUDY 1 - Poor Quality of Life, Depressed Mood, and Memory Impairment may be Mediated by Sleep Disruption in Patients with Addison's Disease

A version of this chapter has been published as a peer-reviewed journal article:

Henry, M., Wolf, P. S. A., Ross, I. L., & Thomas, K. G. F. (2015). Poor quality of life, depressed mood, and memory impairment may be mediated by sleep disruption in patients with Addison's disease. *Physiology and Behavior*, 151, 379-385. DOI: 10.1016/j.physbeh.2015.08.011.

This chapter differs from the original article in that here I have: (1) provided more detail regarding ethical considerations and measures used, (2) used non-parametric statistical tests where appropriate, (3) added statistical analyses of certain quality of life variables that were not reported on in the original article, and (4) added text to the discussion where required by, for instance, those additional statistical analyses.

Abstract

Standard replacement therapy for Addison's disease (AD) does not restore a normal circadian rhythm. In fact, hydrocortisone replacement in patients with AD likely induces disrupted sleep. Given that healthy sleep plays an important role in improving quality of life, optimizing cognition, and ensuring affect regulation, the aim of this study was to investigate whether poor quality of life, mood alterations, and memory complaints reported by patients with AD are associated with their disrupted sleep patterns. Sixty patients with AD and 60 matched healthy controls completed a battery of self-report questionnaires assessing perceived physical and mental health (Short-Form 36), mood (Beck Depression Inventory-II), sleep quality (Pittsburgh Sleep Quality Index), and cognition (Cognitive Failures Questionnaire). A latent variable model revealed that although AD had a significant direct effect on quality of life, the indirect effect of sleep was significantly greater. Furthermore, although AD had no direct effect on cognitive functioning, the indirect effect of sleep was significant. The overall model showed a good fit (comparative fit index = 0.91, root mean square of approximation = 0.09, and standardized root mean square residual = 0.05). Our findings suggest that disrupted sleep, and not the disease per se, may induce poor quality of life, memory impairment, and affect dysregulation in patients with AD. We think that improving sleep architecture may improve cognitive, affective, and physical functioning.

Keywords: Addison's disease, cognition, hydrocortisone, quality of life, sleep

Introduction

AD results from destruction of the adrenal cortex, with subsequent decreased production of glucocorticoids and mineralocorticoids. If left untreated, the disease can be life-threatening. The typical medication regime consists of oral hydrocortisone or alternative preparations to replace cortisol, and mineralocorticoid (fludrocortisone) to control sodium and potassium balance (Ten et al., 2001; Tytherleigh et al., 2004).

Despite current replacement therapy, patients with AD report relatively poor quality of life, with reduced general health perception (both emotional and physical), decreased vitality, memory impairment, increased prevalence of affective disorders, sleep disturbances, and fatigue (Hahner et al., 2007; Løvås et al., 2010; Løvås et al., 2003; Løvås et al., 2002; Thomsen et al., 2006). Despite known and independent relationships between sleep and (a) general health, (b) memory, and (c) mood, no studies in patients with AD have explored contemporaneous associations between these four variables. We postulate that poor sleep in patients with AD is a biological mechanism underlying self-reported disturbances in quality of life, mood, and cognition.

Løvås, Loge, and Husebye (2002) suggest that fatigue is a feature of adrenal failure, that it persists despite replacement therapy, and that it is a major contributor to self-reported impaired health in AD. Patients with AD also demonstrate increased daytime fatigue, which may be a consequence of poor quality of sleep (García-Borreguero et al., 2000). Although few studies report on sleep impairments in AD, patients appear to experience disrupted sleep that is of poor quality (García-Borreguero et al., 2000; Gillin et al., 1974a; Løvås et al., 2003). Løvås, Husebye, Holsten, and Bjorvatn (2003) found that 34% of their sample of patients with AD reported frequent sleep disturbances, including difficulty falling asleep and repeated and early morning awakenings.

Sleep plays important roles in memory consolidation and affect regulation (Diekelmann & Born, 2010). Rapid eye movement (REM) and non-REM sleep provide optimal conditions for consolidation of different forms of memory (Backhaus et al., 2006). Furthermore, REM sleep has a mood regulatory function (Walker, 2009), with research demonstrating that patients with mood disorders have, relative to healthy individuals, altered REM intensity and integrity (Cartwright, Baehr, Kirkby, Pandi-Perumal, & Kabat, 2003). Because cortisol plays a key role in initiating and maintaining these different sleep stages, it has an important influence on the memory consolidation and affect regulation that takes place during normal, healthy sleep (Payne & Nadel, 2004).

Regarding cognitive functioning in AD, a small number of studies report that, even when on replacement therapy, declarative memory is worse in patients than in healthy controls (Henry, Thomas, & Ross, 2014). Increased levels of anxiety and depression have also been reported in AD populations (Hahner et al., 2007). None of these studies, however, explored disrupted sleep as a possible mechanism underlying the observed deficits.

No studies in patients with AD have explored the relationship between sleep and general health, mood, and memory. Our objectives were therefore to characterise self-reported quality of life in a sample of South African patients with AD, and to investigate whether sleep disturbances correlate with poor quality of life, cognitive impairment, and affective dysregulation. We hypothesise that patients with AD will report poor quality of life (marked by impaired cognition and mood alterations), and that this may be explained by sleep disturbances. Our hypothesis is based on literature showing that (a) cortisol plays a key role in sleep maintenance and integrity, (b) sleep plays an important role in cognitive functioning and affect regulation, and (c) hydrocortisone replacement medication used by patients with AD does not restore the natural circadian rhythm and has direct effects on sleep architecture.

Patients and Methods

Research and Ethics

The research ethics committees from the Department of Psychology and Faculty of Health Sciences (HREC REF: 414/2011) at University of Cape Town, both of which adhere to the Declaration of Helsinki, approved the study procedures. Subjects were invited to participate in the study and all participants gave informed consent. The consent form clearly outlined the purpose of the study, what is expected of participants, and that their confidentiality would be ensured and maintained. All participants had the freedom to withdraw their participation at any point. For patients with AD, whether they chose to participate in this study had no influence on their current treatment from their endocrinologist.

There were no risks associated with the questionnaires administered, however if participants felt uncomfortable with any of the questions they were free to not answer those questions or to withdraw from the study at any time. Participants were made aware that there was no financial benefit from participating in this study.

Patients and Healthy Controls

Sixty adult patients with a diagnosis of AD (recruited from the South African Addison's disease (SAAD) database; Ross et al., 2010) completed the self-administered survey described below. The diagnosis of AD was made on the basis of the suggestive clinical presentation, low basal cortisol level and simultaneously elevated ACTH concentration, or, where indicated, a peak cortisol following 250 µg ACTH stimulation, of less than 550 nmol/L associated with a basal raised plasma ACTH, exceeding 10.1 pmol/L. There was confirmed aetiology for 49 of the 60 patients with AD: autoimmune (82%; $n = 40$), idiopathic (12%; $n = 6$), tuberculosis (4%; $n = 2$), and X-linked adrenal hypoplasia (2%;

$n = 1$). For all patients, clinical and demographic data were extracted by interview and from patient folders.

Sixty healthy controls, recruited using advertisements (see Appendix A) placed at the University of Cape Town and in large corporations in the Cape Town metropolitan area, also completed the survey. Control participants were excluded if they had any chronic mental or psychological illnesses since we wanted to obtain data for healthy individuals.

Design

This cross-sectional descriptive study required participants to fill out several questionnaires relating to socio-demographic information, health status/QoL, sleep, mood/affect, and self-reported cognitive complaints. We used a case-control design, matching groups by age, education (within 3 years), sex, ethnicity, and household income. We restricted enrolment to individuals between the ages of 18 and 75 years.

Procedure

A member of the research team systematically inspected the SAAD database and then contacted patients with AD telephonically to invite them to participate. Healthy control participants were enrolled in the study after they responded to advertisements by contacting the research team.

All potential participants received a consent form (see Appendix B) and the study questionnaire in the post, and were asked to return the completed consent form and questionnaires by way of return post. Figure 2 presents the flow of participants through the recruitment and study processes.

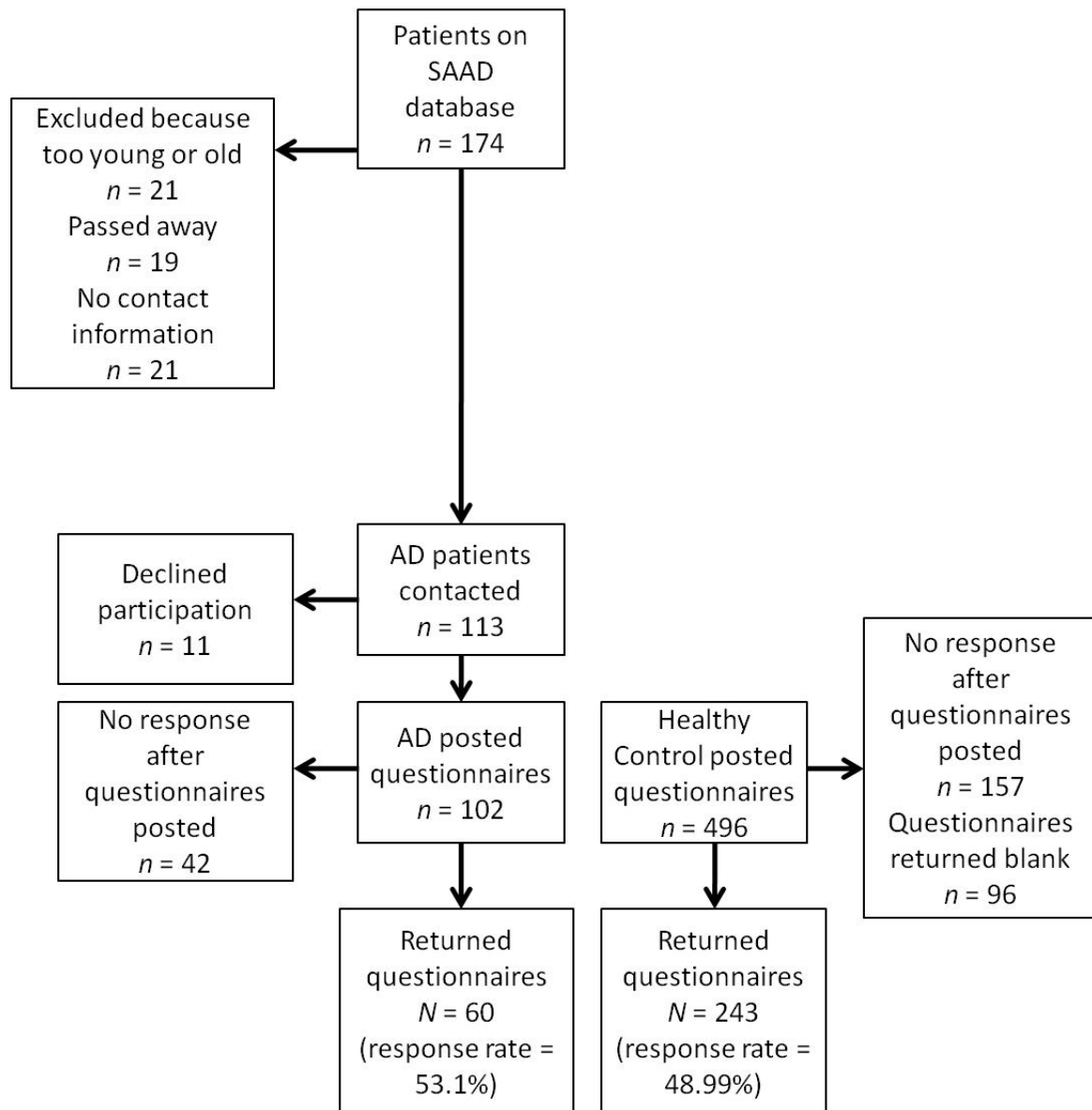


Figure 2. Flow of participants through the recruitment and study processes. To facilitate a case-control design, we selected, based on age, sex, race, and household income. 60 participants from the pool of 243 possible healthy controls. SAAD-South African Addison's disease database, AD-Addison's disease.

Measures

Sociodemographic and medical questionnaire (see Appendix C for AD Group and Appendix D for Healthy Control Group). This measure elicited data about (a) demographic variables (e.g., age, race, household income), (b) medical history, and (c) type and dosage of current medication, and length of time since diagnosis (patients with AD only).

Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; Ware & Sherbourne, 1992). The SF-36 is the most widely used generic instrument to assess health-related subjective health status and assesses eight health-related concepts: a) physical functioning; b) role limitations due to physical health; c) pain; d) general health; e) role limitations due to emotional problems; f) energy/fatigue; g) emotional well-being; h) social functioning. On each of these concepts, the range of scores is 0-100, with higher scores representing better QoL. Four of these concepts (a-d, listed above) are averaged to produce a global Physical QoL score, and the other four (e-h, listed above) are averaged to produce a global Mental QoL score. The SF-36 is a useful tool in assessing a patient's subjective health status as it addresses general health concepts not specific to any age, disease, or treatment group. Furthermore, it has proven a reliable measure of physical and mental health across diverse populations (reliability coefficients ranging from .65 to .94; McHorney, Ware, Rachel, & Sherbourne, 1994).

Beck Depression Inventory-Second Edition (BDI-II; Beck, Steer, & Brown, 1996). The BDI-II is a 21-item self-rated multiple-choice instrument that measures intensity, severity, and depth of depression in respondents. Possible scores range from 0-63, with higher scores representing more depressive symptomatology. The BDI-II is a reliable measure of depression in numerous studies and clinical settings (e.g., Beck, Steer, & Carbin, 1988; Ward, Flisher, Zissis, Muller, & Lombard, 2001), showing high internal consistency ($\alpha = 0.91$) and high 1-week test-retest reliability (Pearson $r = 0.93$), indicating that it is unaffected by daily variations in mood (Beck et al., 1988).

Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989). The PSQI assesses sleep quality and disturbances over the previous 1 month. It comprises 19 items that relate to seven components: sleep quality, sleep latency, sleep duration, sleep disturbances, habitual sleep efficiency, the use of sleeping medication, and

daytime dysfunction due to disrupted sleep. The score on each component ranges from 0-3; hence, the total PSQI score ranges from 0-21, with higher scores representing more disrupted sleep. The PSQI has proven a reliable and valid measure in distinguishing good and poor sleepers. The seven component domains possess high internal consistency (Cronbach's $\alpha = .83$), and the overall questionnaire has a high test-retest reliability (Buysse et al., 1989).

Cognitive Failures Questionnaire (CFQ; Broadbent, Cooper, FitzGerald, & Parkes, 1982). The CFQ is a well-known and frequently used self-report measure of cognitive lapses and slips. It assesses error-proneness with respect to failures in easy cognitive and motor activities (i.e., focusing on failures in typical and habitual behaviour rather than highly demanding and ability-determined actions). The original CFQ developed by Broadbent and colleagues (1982) consists of 25 items. For the current study, the abbreviated CFQ was used (Wilhelm, Witthoft, & Schipolowski, 2010), consisting of 12 items. Participants were instructed to report the frequency of cognitive lapses and slips, over the previous 6 months. Each of the 12 items loads onto one of three factors: *Clumsiness* (i.e., failures related to motor awkwardness, such as bumping into objects inadvertently), *Retrieval* (i.e., failures of both retrospective and prospective memory, such as forgetting to transfer a message to somebody when requested to do so), and *Intention Forgotten* (i.e., failures related to maintaining intentions, such as forgetting what you came to the shops to buy). The CFQ total score ranges from 0-48, with higher scores indicating more impaired cognitive functioning.

Data Management and Statistical Analysis

We scored each of the measures using standard procedures, detailed in the relevant scoring manuals. After comparing sample characteristics and between-group comparisons, we examined zero-order correlations using Pearson's r correlation coefficients, and created latent variable models to test predictions about the direction and strength of relationships between AD, quality of life, sleep, and cognition. Specifically, we hypothesised that these

four latent variables would relate to one another in the way depicted in Figure 3. Regarding the manifest variables in that figure: We included in our modelling (a) in the case of the SF-36, two composite variables (Physical and Mental), each of which summarized four of the instrument's eight subscales; and (b) in the case of the PSQI, three variables (subjective sleep quality, sleep efficiency, and sleep disturbance) that, both empirically and theoretically, best described sleep disruptions in this sample.

Figure 3, then, shows the set of hypotheses we wished to examine (solid lines), as well as plausible alternative hypotheses (dashed lines). We created a latent variable model to describe the complete set of relationships (both dashed and solid lines) depicted in Figure 3; then, we created a second model to describe the set of relationships depicted by the solid lines only in Figure 3. In other words, this second model removed parameters that, initially, represented plausible alternative hypotheses. We compared the two models to see which provided the best fit for the data.

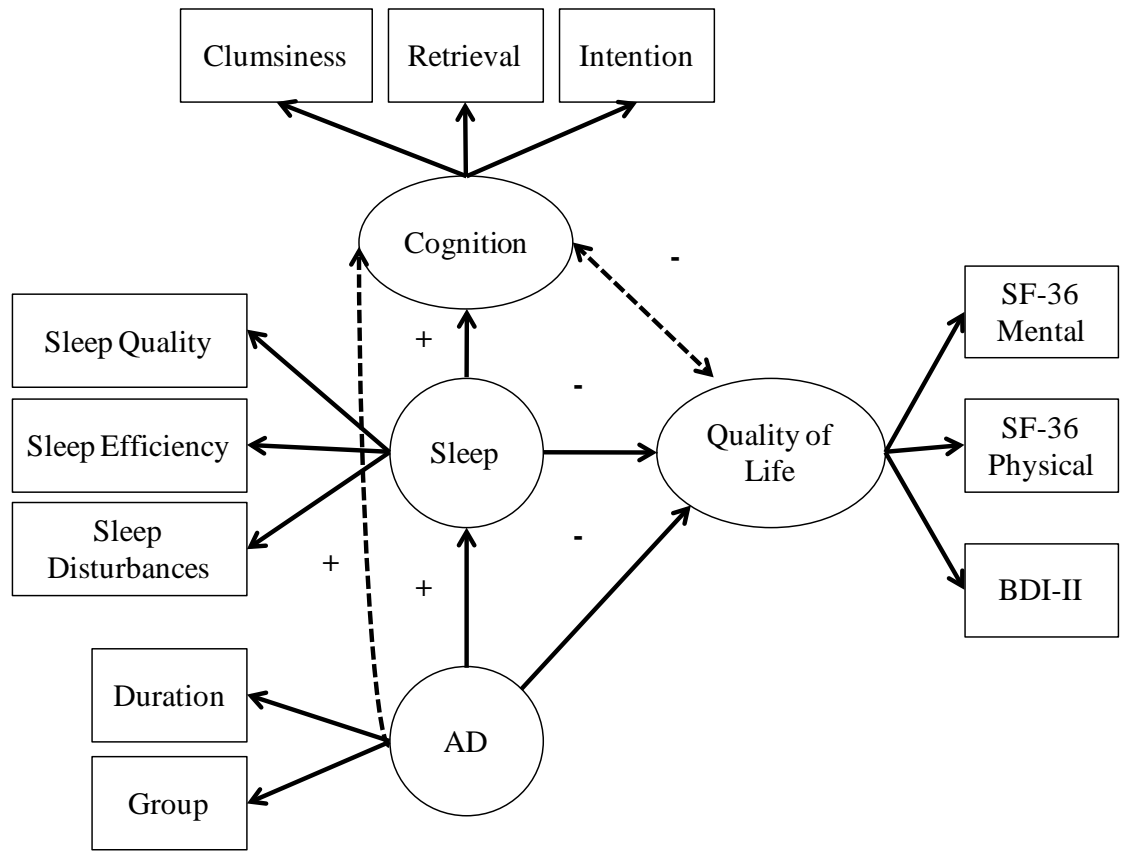


Figure 3. Initial latent variable model showing hypotheses we wished to examine (represented by solid lines) and plausible hypotheses (dashed lines). Plus signs (+) indicate a positive relationship, whereas minus signs (-) indicate a negative relationship. We predicted that having Addison's disease would result in poorer sleep (represented by higher scores on the Pittsburgh Sleep Quality Inventory), and poorer quality of life (represented by lower scores on the SF-36 Mental and Physical scales and higher scores on the BDI-II scale). We also predicted that having poorer sleep (i.e., higher PSQI scores) would result in worse cognition (i.e., higher CFQ scores) and poorer quality of life (i.e., lower SF-36 scores). Finally, we predicted that having Addison's disease may result in impaired cognition, and that poorer cognition (i.e., higher CFQ scores) may result in poorer quality of life (i.e., lower SF-36 scores), or vice-versa.

Regarding sample size, conventional guidelines suggest that a minimum of 5 participants is required for every free parameter included in a model (Bentler & Chou, 1987). It is possible to run latent variable models with 100 participants (Gorsuch, 1983). Obtaining larger samples can be challenging when studying rare diseases such as AD, which has a global population prevalence of 39-117 per million (Løvås & Husebye, 2002), and a prevalence in South Africa of 3.1 per million (Ross & Levitt, 2013). We believe, given our

population of study, there were a sufficient number of participants in our final sample ($N = 120$).

We completed all analyses using R (the `sem` package), and SPSS (Version 22).

Unless noted otherwise, we set the threshold for statistical significance (α) at .05.

Results

Sample Characteristics

Table 1 presents the clinical characteristics of patients with AD. Of note is that six participants (one man aged 37 years, and five women aged 21, 38, 47, 50, and 64 years, respectively) were prescribed prednisone; the remainder were prescribed hydrocortisone. The average daily prednisone dose was 9.06mg ($SD = 4.01$), and the average daily prednisone/kg dose was 0.12mg/kg ($SD = 0.08$).

Overall, the patients and controls were matched for age (AD: $M = 50.57 \pm 14.37$ years, range = 20-74 years; controls: $M = 49.90 \pm 14.70$ years, range = 19-77 years; $p = .792$), sex distribution (14 males and 46 females in each group), ethnicity distribution (53 white, 2 Asian, and 5 coloured [mixed black-white ancestry] individuals in each group), education (AD: $M = 13.62 \pm 2.53$ years, range = 8-20 years; controls: $M = 14.42 \pm 2.84$ years, range = 10-22 years; $p = .118$), and monthly household income ($p = .504$). Table 1 also shows that, there were no between-group differences in terms of BMI (AD: $M = 26.60 \pm 6.13$ kg/m², range = 18.37-42.19 kg/m²; controls: $M = 24.82 \pm 4.02$ kg/m², range = 18.20-37.81 kg/m²; $p = .151$). In patients with AD, the most prevalent co-morbid illnesses were primary hypothyroidism (30%, $n = 18$ patients) and diabetes mellitus (20%, $n = 12$ patients).

Table 1
Sample Characteristics (N = 120)

Variable	Addison's Disease (<i>n</i> = 60)	Healthy Controls (<i>n</i> = 60)	<i>t</i> / χ^2	<i>p</i>	ESE
Age at diagnosis (years) ^a	31.03 (14.41) 3-67				
Duration of AD (years) ^a	19.33 (13.34) 1-54				
Total hydrocortisone dose ^b	22.02 (7.23) 5-35				
Hydrocortisone/kg ^c	0.31 (0.14) 0.10-0.70				
Number of doses per day ^d	1.95 (0.70) 1-3				
Concurrent co-morbid diseases	1.63 (1.71) 0-7				
Age	50.57 (14.37) 20-74	49.90 (14.70) 19-77	-0.26	.792	0.05
Body mass index*	26.60 (6.13) ^f 18.37-42.19	24.82 (4.02) ^h 18.20-37.81	1103	.151	0.14
Education	13.62 (2.53) ^g 8-20	14.42 (2.84) ⁱ 10-22	1.58	.118	0.30
Income (in ZAR) ^e			4.33	.504	0.20
1000-2499	4	1			
2500-5499	8	6			
5500-9999	11	7			
10000-19999	10	10			
20000-30000	7	11			
> 30000	15	19			

Note. Body mass index was calculated by dividing the participant's weight by height² (information obtained from the sociodemographic questionnaire). For all of the variables except *Income*, means (with standard deviations in parentheses) are presented on the top line, and range is presented below that. Regarding the variable *Income*, ZAR = South African rands; when the study was conducted, the ZAR:US\$ exchange rate was 8.65:1. For that variable, actual numbers of participants in each cell are presented. ESE = effect size estimate; in this case, Cohen's *d* (for the *t*-tests), or Cramer's *V* (for the χ^2 test).

^aData based on 58 participants. ^bData based on 52 participants; 2 patients did not provide the relevant answers on the sociodemographic questionnaire, and the remaining 6 were prescribed prednisone. ^cData based on 51 participants; 3 patients did not provide the relevant answers on the sociodemographic questionnaire, and the remaining 6 were prescribed prednisone. ^dData based on 59 participants. ^eData based on 55 participants in the AD group and 54 participants in the control group. ^fData based on 48 participants. ^gData based on 58 participants. ^hData based on 55 participants. ⁱData based on 55 participants.

*Mann Whitney *U* test performed. In this case, test statistic = *U*, effect size = *r*.

Between-group Comparisons: Patients versus Controls

Table 2 presents the results of Mann-Whitney U non-parametric tests comparing the scores of patients with AD and healthy controls on all measures of quality of life, depression, sleep disruption, and cognitive functioning. Even after the Bonferroni correction to control for inflated familywise error associated with multiple comparisons (in this case, $\alpha = .05/22 = .002$), most between-group differences remained statistically significant. Patients reported poorer quality of life, more depressive symptomatology, more disrupted sleep, and more cognitive impairment than controls.

Latent Variable Models

We utilized statistical models that sought to determine the set of relationships between our latent variables: AD (estimated by its presence or absence, and its duration), sleep disruption (estimated by three components on the PSQI), quality of life (estimated by two components on the SF-36 plus the BDI-II), and cognition (estimated by three components on the CFQ). Table 3 presents the correlations among manifest variables.

We utilized a two-step procedure. First, we tested a measurement model, using confirmatory factor analysis (CFA), and then we tested two structural causal models designed to test theory. In all three models, most of the fit indices reflected adequate fit.

Measurement model. Our model estimated the relationships between four hypothesized latent variables (AD, sleep disruption, quality of life, and cognition). Figure 4 summarizes the results of the measurement model. The CFA fit well according to all but one of the tested fit indices; only the χ^2 statistic was statistically significant. This statistic is used to test the null hypothesis that the model fits the data, and hence its statistical significance might be a cause for concern. However, this statistic is quite sensitive to sample size and to departures from multivariate normality, and often rejects otherwise well-fitting models (Hatcher, 1994).

Table 2

Self-reported Quality of Life, Depression, Sleep Quality, and Cognitive Functioning
(*N* = 120)

Variable	Addison's Disease (<i>N</i> = 60)	Healthy Controls (<i>N</i> = 60)	<i>U</i>	<i>p</i>	ESE
SF-36					
Physical	67.58 (28.58)	89.33 (18.97)	874.00	< .001**	0.45
Role Limitations - Physical	62.5 (41.69) ^a	92.50 (22.22)	1011.50	< .001**	0.43
Role Limitations - Emotional	62.22 (43.17)	93.89 (20.81)	1082.50	< .001**	0.43
Energy	48.53 (22.18) ^a	67.45 (14.36) ^a	826.50	< .001**	0.44
Emotional	68.48 (19.50)	81.83 (9.89)	1054.50	< .001**	0.36
Social	72.73 (27.48)	92.92 (12.47)	970.00	< .001**	0.42
Pain	65.63 (32.36)	88.13 (15.51)	1042.50	< .001**	0.38
General Health	50.20 (24.01)	78.05 (14.17) ^b	601.50	< .001**	0.57
Overall Physical	61.08 (26.83) ^a	87.04 (12.48) ^b	594.00	< .001**	0.56
Overall Mental	62.49 (22.60) ^a	83.98 (10.84) ^a	634.50	< .001**	0.54
BDI-II	12.36 (10.27) ^a	3.37 (3.76)	639.50	< .001**	0.55
PSQI					
Sleep Quality	1.18 (0.93)	0.72 (0.61)	1307.50	.005*	0.26
Sleep Latency	1.28 (1.13)	0.71 (0.87) ^b	1277.00	.006*	0.25
Sleep Duration	1.02 (0.87)	0.72 (0.56)	1507.00	.085	0.41
Sleep Efficiency	0.93 (1.06)	0.42 (0.67)	1328.50	.006*	0.25
Sleep Disturbances	1.42 (0.70)	0.97 (0.52)	1193.50	<.001**	0.30
Use of sleep medication	1.02(1.40)	0.20 (0.55)	1306.00	< .001**	0.31
Daytime dysfunction	1.02 (0.85)	0.50 (0.50)	1200.00	<.001**	0.75
Total	7.87 (4.89)	4.20 (2.47)	930.50	<.001**	0.41
CFQ					
Clumsiness	4.12 (3.68)	2.75 (2.17)	1497.50	.109	0.15
Intention Forgotten	3.17 (2.66)	2.08 (1.73)	980.00	.037*	0.19
Retrieval	8.46 (4.30) ^b	5.15 (3.40)	1408.50	< .001**	0.39

Note. SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; BDI-II = Beck Depression Inventory-Second Edition; PSQI = Pittsburgh Sleep Quality Index; CFQ = Cognitive Failures Questionnaire; ESE = effect size estimate; in this case, *r*.

^aData based on 58 participants.

^bData based on 59 participants.

p* < .05. *p* < .002 (i.e., statistically significant after the Bonferroni correction).

Structural model. The two theoretical models we tested (see Figure 3) were identical except that one (indicated using dashed lines) included two plausible alternative causal hypotheses. These two hypotheses were not predicted by the theory being tested, but served as alternatives that could have either disconfirmed the theory or provided evidence that it was

not complete. The more inclusive model had adequate fit, but the two alternative causal paths were not statistically significant, with a standardized path coefficients of -0.147 , $p = .160$ (the causal pathway connecting cognition to quality of life) and 0.05 , $p = .640$ (the causal pathway connecting AD to cognition). Hence, the final model omitted these non-significant causal pathways and fit just as well (see Figure 4).

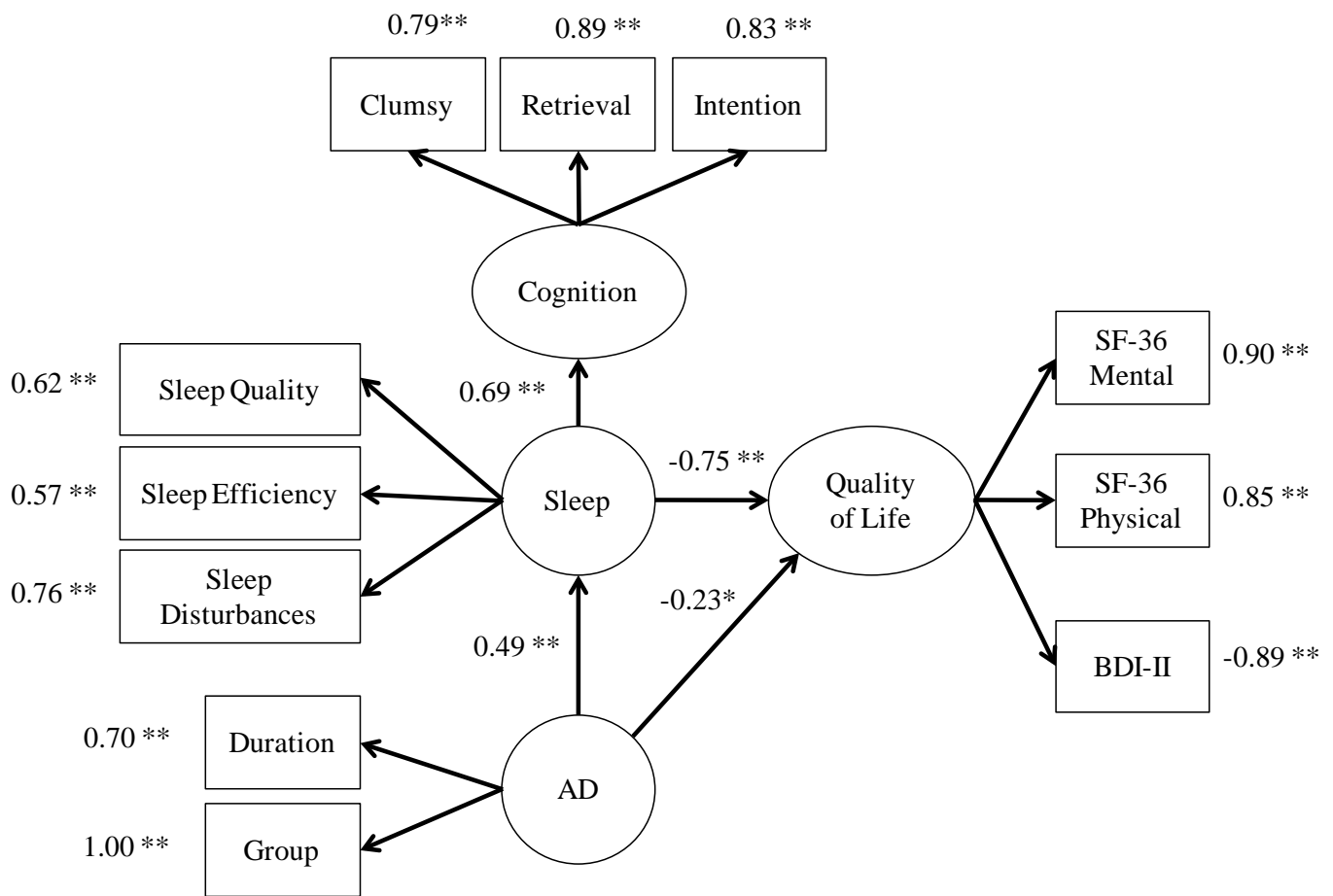


Figure 4. Measurement model. Model chi-square = 74.97406, $df = 38$, $p = .0003$, Goodness-of-fit index = 0.91, Root-means-square error of approximation (RMSEA) = 0.09, Bentler-Bonett Normed Fit Index (NFI) = 0.91, Bentler Comparative Fit Index (CFI) = 0.95, Bentler Relative Noncentrality Index (RNI) = 0.95, Bollen Incremental Fit Index (IFI) = 0.95, Standardized Root Mean Square Residual (SRMR) = 0.05.

* $p < .05$. ** $p < .01$.

Table 3

Correlation Matrix for All Manifest Variables Included in the Latent Variable Models (N = 120)

Variable	1	2	3	4	5	6	7	8	9
1. SF-36: Physical	1.00								
2. SF-36: Mental	0.778**	1.00							
3. BDI-II	-0.733**	-0.797**	1.00						
4. PSQI: Sleep Quality	-0.459**	-0.458**	0.458**	1.00					
5. PSQI: Sleep Efficiency	-0.365**	-0.320**	0.438**	0.459**	1.00				
6. PSQI: Sleep Disturbances	-0.597**	-0.527**	0.589**	0.506**	0.414**	1.00			
7. CFQ: Clumsiness	-0.426**	-0.465**	0.436**	0.331**	0.290**	0.368**	1.00		
8. CFQ: Retrieval	-0.460**	-0.555**	0.511**	0.296**	0.323**	0.489**	0.675**	1.00	
9. CFQ: Intention Forgotten	-0.391**	-0.459**	0.356**	0.276**	0.348**	0.452**	0.668**	0.732**	1.00

Note. Values presented are Pearson's r correlation coefficients. SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; BDI-II = Beck Depression Inventory-Second Edition; PSQI = Pittsburgh Sleep Quality Index; CFQ = Cognitive Failures Questionnaire.

** $p < .01$.

Additional Analyses

We sought to determine whether certain demographic and disease characteristics played a role in determining outcome variable scores. Such information may be useful in establishing (a) across the sample, whether individual differences affected quality of life, and (b) within the sample of patients with AD, which disease characteristics affected quality of life.

First, a series of independent-samples *t*-tests sought to determine whether, within each group separately, sex had a significant influence on the outcome variable scores. The analyses detected three significant sex differences within the AD group: On average, male patients with AD reported, on the SF-36, (a) better physical health (men: $M = 81.07 \pm 26.18$, women: $M = 63.48 \pm 28.26$); $t(58) = 2.07$, $p = .043$, $d = 0.65$), and (b) higher energy levels (men: $M = 60.77 \pm 18.58$, women: $M = 45.00 \pm 22.05$); $t(56) = 2.36$, $p = .023$, $d = 0.77$). In addition, on average, male patients with AD reported, on the PSQI, shorter sleep duration (men: $M = 0.57 \pm 0.76$, women: $M = 1.15 \pm 0.87$); $t(58) = -2.25$, $p = .028$, $d = 0.71$) than their female counterparts.

The analyses also detected two significant sex differences within the control group: On average, male controls reported, on the PSQI, (a) a greater number of sleep disturbances (men: $M = 1.21 \pm 0.43$, women: $M = 0.89 \pm 0.53$); $t(58) = 2.09$, $p = .041$, $d = 0.63$), and (b) shorter sleep duration (men: $M = 1.00 \pm 0.68$, women: $M = 0.63 \pm 0.49$); $t(58) = 2.26$, $p = .028$, $d = 0.62$) than their female counterparts.

Second, correlational analyses sought to determine whether, within each group separately, age had a significant influence on the outcome variable scores. Among controls, increasing age was associated with worse scores on the SF-36 Overall Physical ($r = -0.27$, $p = .036$), CFQ Retrieval ($r = 0.29$, $p = .023$), and CFQ Intention Forgotten ($r = 0.35$, $p = .005$) scales, and shorter sleep latency ($r = -0.26$, $p = .044$). In the AD group, increasing age was

associated with worse scores on the SF-36 Physical Functioning subscale ($r = -0.41, p = .001$), and PSQI Sleep Disturbances ($r = 0.30, p = .022$) scales.

Third, correlational analyses sought to determine whether, in the AD group, there were significant associations between disease characteristics and outcome variable scores. These analyses suggested that duration of illness was associated with worse scores on the SF-36 Physical Functioning subscale ($r = -0.23, p = .046$), PSQI Sleep Disturbances ($r = 0.23, p = .044$) and PSQI Daytime Dysfunction ($r = 0.25, p = .032$). Total hydrocortisone dose was associated with worse scores on PSQI Sleep Quality ($r = 0.28, p = .024$), PSQI Sleep Latency ($r = 0.31, p = .014$), and PSQI Total Scores ($r = 0.26, p = .031$). Neither dosage/kg nor number of doses per day correlated significantly with any of the outcome scores.

Fourth, a series of Fisher's Exact Tests sought to determine whether, in the AD group, there was an association between timing of the last dose (before noon, $n = 18$; between noon and 18h00, $n = 16$; after 18h00, $n = 20$; 6 patients with AD did not report on the timing of their last dose of the day) and outcome variable scores. The analyses suggested that timing of the last dose was associated with scores on (a) the SF-36 Overall Physical scale, $p < .001$, (b) the BDI-II, $p = .019$, and (c) PSQI Sleep Duration scale, $p = .013$. Overall, these analyses suggested that (a) patients who took their last dose after 18h00 were more likely to report poor QoL (see Figure 5), (b) patients who took their last dose before noon or after 18h00 were more likely to report severe depression (see Figure 6), and (c) patients who took their last dose after 18h00 were more likely to report shorter sleep duration (see Figure 7).

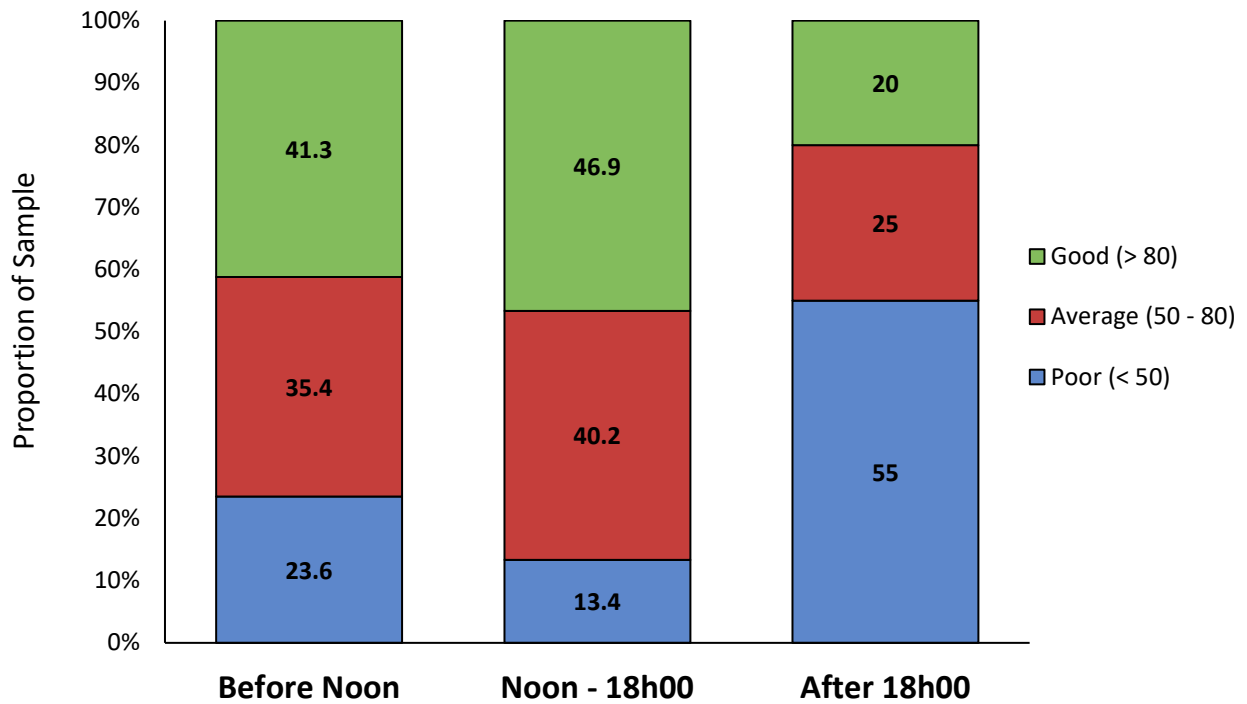


Figure 5. Overall physical health (as measured by the SF-36) of patients with AD, stratified by timing of last dose.

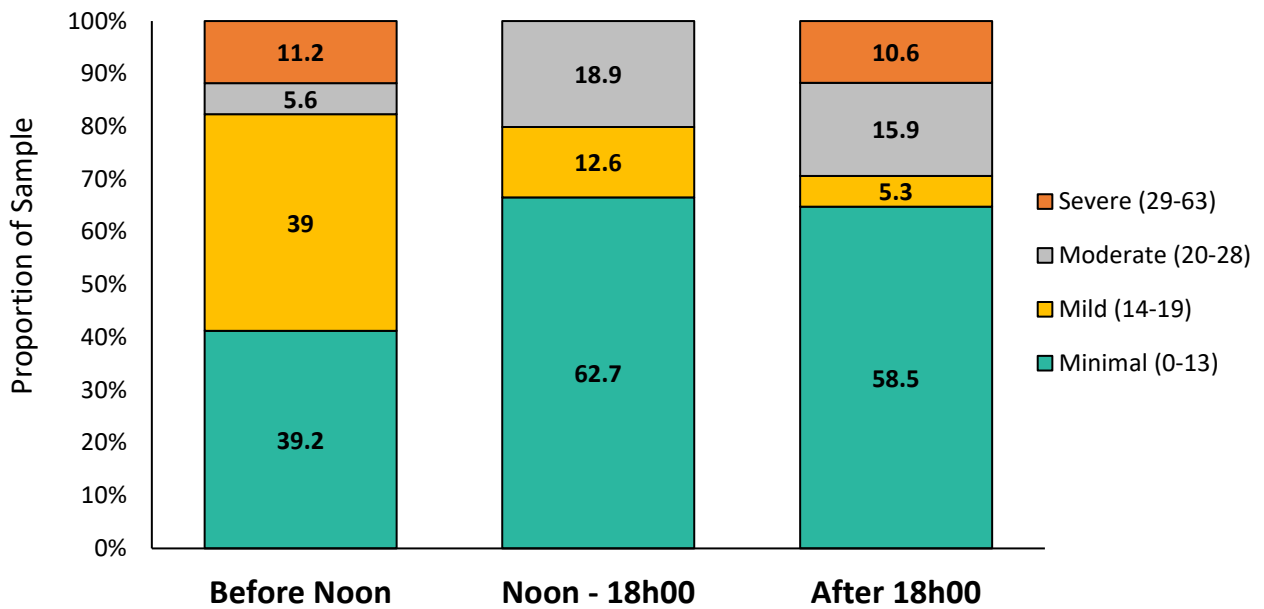


Figure 6. Depressive symptomology (as measured by the BDI-II) of patients with AD, stratified by timing of last dose.

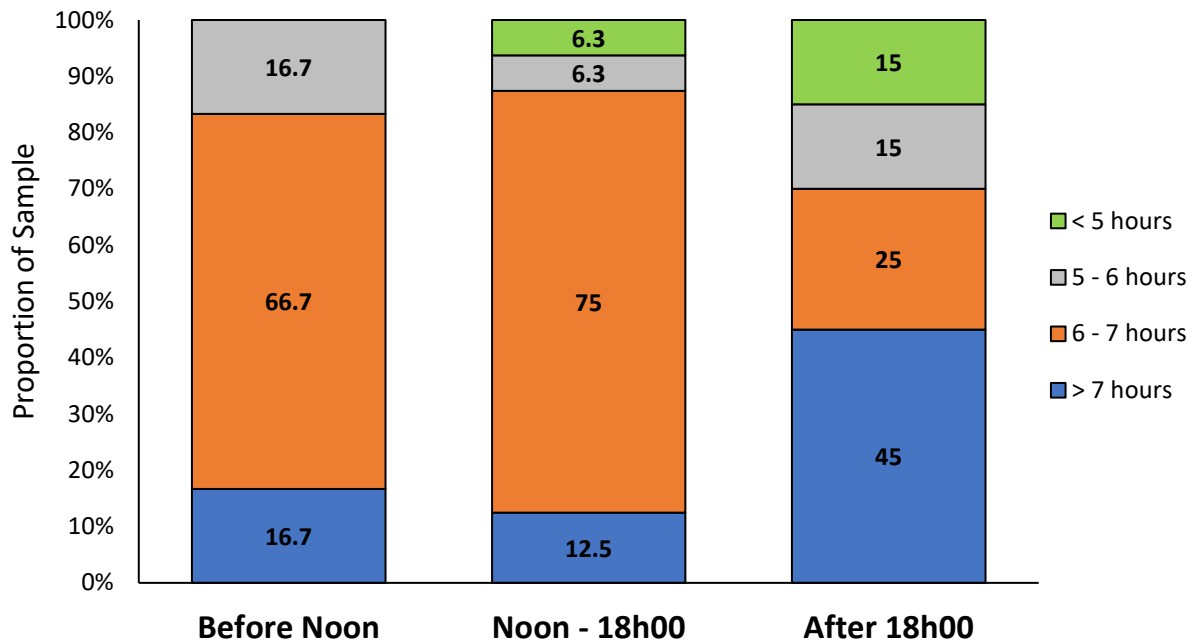


Figure 7. Sleep duration (as measured by the PSDQI) of patients with AD, stratified by timing of last dose.

Finally, we wished to determine whether, within the AD group, the character of certain co-morbid illnesses influenced outcome scores. Because the most common co-morbid diseases were hypothyroidism (present in 18 patients) and diabetes (present in 12 patients), separate independent samples *t*-tests compared scores on the outcome variables in patients who had hypothyroidism versus those who did not, and in patients who had diabetes versus those who did not. Regarding the hypothyroidism comparison, there were no significant between-group differences (all *p*'s > .105). However, the presence of diabetes was associated with better self-reported mental health (SF-36 Mental: $t(56) = 2.06, p = .044, d = 0.69$), lower levels of depression (BDI-II: $t(56) = -2.41, p = .019, d = 0.78$), and better sleep quality (PSQI Sleep Disturbances: $t(58) = -3.50, p = .002, d = 0.95$).

Discussion

A cohort of South African patients with AD reported poorer quality of life, increased mood disturbance, more disrupted sleep, and a greater degree of memory impairment than matched healthy controls. Our data are consistent with previous European studies suggesting that, despite being on replacement therapy, patients with AD report experiencing poor quality of life (Hahner et al., 2007; Løvås et al., 2002). The novel contribution of this study, however, is that it links disrupted sleep and poor quality of life in patients with AD to both cognitive and affective dysregulation. Using a series of latent variable models, we describe specific associations between sleep, affect, memory, and quality of life in AD. These models suggested that (a) the indirect effect of sleep disturbances on quality of life was greater than that of disease status, and (b) the presence of AD did not directly influence cognition; however, (c) the relationship between AD and cognition was significant when mediated by sleep. Hence, we suggest that sleep disturbances are a plausible, but not yet confirmed, biological mechanism underlying poor quality of life, mood disturbances, and impaired cognitive functioning in patients with AD.

Sleep has a restorative function on the body (both physically and neurologically), and sleep and circadian rhythms play an important role in daily physiological functions (Depner, Stothard, & Wright Jr, 2014). Disrupted sleep and circadian rhythms attenuate quality of life and well-being (Winzler et al., 2014), and lead to energy imbalances, metabolic dysregulation, and fatigue (Depner et al., 2014). Hence, it is not surprising that patients with AD who report frequent sleep disturbances and reduced sleep quality also experience poorer subjective health, fatigue, and reduced vitality.

A plethora of research has shown that both SWS and REM sleep, and the successful transition between these sleep stages, is vital for healthy memory consolidation across the night (Backhaus et al., 2006). Cortisol plays a vital role in ensuring the smooth transition from one sleep stage to the next (Stickgold, 2011). Patients with AD on replacement therapy show patterns of cortisol secretion that are non-physiological: They experience lower than normal cortisol concentrations in the early hours of the morning and before taking their medication, and experience a peak in cortisol levels soon after medication ingestion. They may also have higher-than-normal cortisol levels prior to sleep onset and in the early hours of the sleep cycle (Harbeck et al., 2009).

Previous studies suggest that replacement regimens may have a direct influence on the sleep architecture of patients with AD. For instance, García-Borreguero et al. (2000) reported that patients with AD who took hydrocortisone before bedtime had significantly decreased REM latency and increased REM sleep time; in contrast, and in confirmation of previous results (Gillin et al., 1974a), those who were deprived of glucocorticoid medication 1.5 hours prior to bedtime showed increased REM latency and decreased REM sleep time.

The extant literature has not, however, explored the implications for cognition and for overall quality of life, of these altered circadian cortisol patterns, and of consequent disrupted sleep architecture, in patients with AD. Although previous studies have shown that patients with AD self-report sleep disruptions and experience memory impairment (Henry et al., 2014; Løvås et al., 2003), we show a definite association between sleep disruption and memory impairment.

Similarly, previous studies have found, as we did, that patients with AD experience more symptoms of affective disorder than do healthy controls (Hahner et al., 2007; Thomsen et al., 2006), but no published study has explored the relationship between affect dysregulation and

sleep disturbances in AD. It is our contention that disrupted sleep is a key biological mechanism underlying depressed mood in patients with AD. In general, depressed patients self-report sleep disturbances (e.g., difficulty falling and staying asleep, and early morning awakenings; Almeida & Pfaff, 2005), and on polysomnographic measure appear to experience both SWS and REM disruptions (Cartwright et al., 2003). Following treatment for depression, mood improves after REM sleep is selectively inhibited (Cartwright et al., 1998). Of interest here is that individuals who take hydrocortisone before bedtime have significantly decreased REM latency and increased REM sleep time, a pattern similar to that found in depressed patients. Hence, altered circadian rhythms in patients with AD may explain the high presence of affective disorders in this population.

Consistent with previous studies, in the current patient cohort, hydrocortisone dose per kg and number of doses per day did not impact on measures of quality of life, sleep disruption, mood, and cognition (Bleicken et al., 2010). However, longer disease duration was associated with worse physical health, increased sleep disturbances and daytime dysfunction due to sleep disturbances. Since prolonged exposure to synthetic corticosteroids is known to impact QoL and sleep (Bleicken et al., 2010; Ragnarsson et al., 2014; Steiger, 2003), this result is not surprising given that longer disease duration equates to a longer period of time using replacement medication. Furthermore, patients taking higher doses of hydrocortisone reported poorer sleep quality and longer sleep latency, patients who took their last dose of medication after 6pm reported worse quality of life, being more depressed, and sleeping for shorter periods of time, and patients who took their last dose of medication before noon (i.e., they only took one dose per day) reported being more depressed. These results are in concordance with previous studies suggesting that (a) higher doses of HC or doses taken later in the day result in worse health and

QoL (Bleicken et al., 2010; Florkowski, Holmes, Elliot, Donald, & Espiner, 1994; Jódar, Valdepeñas, Martinez, Jara, & Hawkins, 2003; Ragnarsson et al., 2014) and sleep (Løvås et al., 2003; Steiger, 2003), and (b) a twice or thrice daily regimen is more optimal compared to a single daily dose (Bleicken et al., 2008; Mah et al., 2004).

Counterintuitively, however, patients with AD with diabetes reported significantly fewer sleep disturbances, better mental health, and lower levels of depression than those without. This unexpected finding cannot be explained by between-group differences with regard to clinical or sociodemographic characteristics: The patient groups with and without diabetes were not significantly different in terms of, for instance, age, age at diagnosis, duration of illness, BMI, and number of doses per day. Hence, there remain at least two possible explanations for the observed pattern of data. The first is that the statistical analyses have produced a Type I error. The likelihood of such an error arising is particularly strong given the unequal sample sizes, and the small size of the diabetes group ($n = 12$). A second possible explanation for our findings, however, is that patients with AD with diabetes report better mental health and lower levels of depression because they experience less disturbed sleep. This explanation would be consistent with our findings that sleep plays an important role in quality of life. This finding requires replication; certainly, the current data do not permit speculation as to causal direction, and, as noted above, we cannot rule out the possibility of a Type I error.

Regarding the effects of demographic variables on the measured outcomes, our findings are consistent with known associations between advancing age and poorer physical well-being, increased cognitive impairment, and increased sleep disturbances. Consistent with previous studies reporting that women with AD have more impaired quality of life than their male counterparts (Kluger et al., 2014), we found that our male patients reported better physical health

and higher energy levels than their female counterparts. Furthermore, in both our AD and Control groups, males reported shorter sleep duration. This result may be spurious given our relatively small N of men in each group.

Limitations

A major limitation of our study is the lack of objective measurements. Although our results suggest that disrupted sleep is a mechanism underlying poor quality of life, impaired memory, and affective dysregulation in patients with AD, all of the information is self-reported; to corroborate our findings, studies using objective measures should be conducted. For instance, the specific memory deficits experienced by patients with AD must be assessed using standardized neuropsychological instruments. Similarly, polysomnograph studies are needed to confirm the presence, and nature, of disrupted sleep architecture in patients with AD.

Another limitation of our study is its small sample size, particularly in relation to the statistical analyses we used. However, sample size in structural equations modelling is a complex topic on which there is no general consensus. Estimates for minimum sample size range from 50 to 500 participants (Iacobucci, 2010). The larger estimates ensure sufficient statistical power, generalizability, and accuracy of parameter estimates across a range of conditions that impact statistical power. To get the most out of our rare participants we used reliable measures, tested a relatively simple model, and shied away from empirically modifying the models a posteriori. These tactics maximized statistical power in our relatively small sample. In such cases, it has been argued that 100 participants are sufficient to obtain a convergent solution.

Moreover, our small patient population was extremely heterogeneous. They were sampled across a large age range; some women had experienced menopause, and others were

using oral contraceptives; and they were not screened for neuropsychiatric illness. All of these variables might affect sleep quality and architecture (Kirschbaum et al., 1999).

Finally, we note that our results might have been influenced by the presence of survivor and volunteer biases in our sample. Regarding the former, 19 of the 174 patients registered in the SAAD database had died before the onset of our study. We have no information about these individuals' cause of death, or about their quality of life, mood, sleep, and cognition in the years preceding their death. Regarding possible volunteer biases, 11 potential patients with AD declined involvement in the study, 42 did not respond after a questionnaire had been posted to them, and 21 were not contactable. Again, we have no information about why these individuals either were not willing to participate, or why the database contained no accurate contact information for them. There did not appear to be any systematic reason (e.g., age, race/ethnicity, language, time since diagnosis) for these individuals' non-participation, however.

Conclusion

In summary, we found that, consistent with previously published studies, South African patients with AD report poorer quality of life, sleep quality, mood, and cognition than matched healthy controls. The novel contribution of our study, however, is that it reports data suggesting that disrupted sleep may be a biological mechanism underlying the abovementioned deficits. Intervention studies and clinical trials might seek to confirm this suggestion. Such confirmation has important implications for the treatment of AD, in that it will encourage health professionals to identify whether disrupted sleep is present, and to prioritize its treatment.

CHAPTER FOUR
STUDY 2 - Episodic Memory Impairment in Addison's Disease:
Results from a Telephonic Cognitive Assessment

A version of this chapter has been published as a peer-reviewed journal article:

Henry, M., Thomas, K. G. F., & Ross, I. L. (2014). Episodic memory impairment in Addison's disease: results from a telephonic cognitive assessment. *Metabolic Brain Disease*, 29 (2), 421-430. DOI: 10.1007/s11011-014-9511-x.

This chapter differs from the original article in that here I have: (1) reported on data analyses of a larger sample size ($n = 35$ per group, rather than $n = 27$ per group; note that this increase in sample size is because more data were collected post-publication, and that the increase has not changed the pattern or interpretation of data as originally reported); (2) provided more detail regarding ethical considerations; (3) added statistical analyses using a different scoring method; (4) added statistical analyses involving certain demographic and disease characteristics (viz., age, sex, education, income, depressive symptomology, and time of last hydrocortisone dose), and (5) added text to the discussion where required by, for instance, those additional statistical analyses.

Abstract

Patients with Addison's disease (AD) frequently self-report memory and attention difficulties, even when on standard replacement therapy. However, no published study examines, using objective measures and assessing across multiple domains, the cognitive functioning of patients with AD relative to healthy controls. The primary aim of this study was to investigate whether the previously reported subjective cognitive deficits in AD are confirmed by objective measures. Conducting comprehensive neuropsychological assessments of patients with relatively rare clinical disorders, such as AD, is challenging because access to those patients is often limited, and because their medical condition might prevent extended testing sessions. Brief telephonic cognitive assessments are a useful tool in such circumstances. Hence, we administered the *Brief Test of Adult Cognition by Telephone* to 35 patients with AD and 35 matched healthy controls. The instrument provides objective assessment of episodic memory, working memory, executive functioning, reasoning, and speed of processing. Statistical analyses confirmed that patients performed significantly more poorly than controls on the episodic memory subtest. There were, however, no significant between-group differences on the attention, executive functioning, reasoning, and speed of processing subtests. Patients with an older age at diagnosis performed more poorly across nearly all domains of cognition. Furthermore, older age was associated with worse cognitive functioning in both patients and controls. We conclude that, for patients with AD, previously reported subjective cognitive deficits are matched by objective impairment, but only in the domain of episodic memory. Future research might investigate (a) whether these memory deficits are material-specific (i.e., whether non-verbal memory is also affected), and (b) the neurobiological mechanisms underlying these deficits.

Keywords: telephonic cognitive assessment, Addison's disease, memory, Brief Test of Adult Cognition by Telephone, cognition

Introduction

AD is a rare endocrine disorder that typically results from destruction of the adrenal cortex, and that is characterized by decreased production of glucocorticoids and mineralocorticoids. Despite replacement therapy (usually oral hydrocortisone or prednisone to replace cortisol, plus an additional mineralocorticoid (fludrocortisone) to control sodium and potassium balance), patients frequently report experiencing relatively poor quality of life (Hahner et al., 2007; Løvås et al., 2010; Løvås et al., 2003; Løvås et al., 2002; Thomsen et al., 2006). In particular, and aside from reports of reduced vitality, sleep disturbances, and increased fatigue and affective problems, these patients often complain of poor memory and impaired concentration (Arlt, 2009; Ten et al., 2001; Tytherleigh et al., 2004). However, few studies have provided detailed characterization, via objective testing, of cognitive function in AD.

Because of the close relationship between variations in cortisol levels and performance on tests of memory and attention/executive functioning (Lupien et al., 2008; Newcomer et al., 1999; van den Bos, Harteveld, & Stoop, 2009), objective assessment of patients with AD's performance in these domains is particularly pertinent. Previous studies have shown, in healthy young and older adults, that elevated cortisol levels impair cognitive functioning in ways that are predictable and that can be explained at the neurobiological level (Kim & Diamond, 2002; Lupien, Nair, et al., 1999; Sapolsky et al., 1986; Smeets, 2011). These studies focus strictly on psychosocially or pharmacologically induced *elevations* in cortisol levels; in AD, cortisol levels can be elevated far above basal levels (e.g., immediately following hydrocortisone administration) or depressed far below those levels (e.g., when several hours have passed since hydrocortisone administration--the medication has a relatively short half-life of approximately 1.5 hours; Harbeck et al., 2009).

Furthermore, patients with AD do not exhibit the normal diurnal cortisol variation. Healthy individuals have a clear diurnal rhythm in which cortisol levels begin to rise in the early hours of the morning, surge post-awakening, and decrease steadily throughout the day (e.g., from 16h00 to 24h00, cortisol decreases continually until reaching a nadir that is at less than 75% of the morning values; Krieger, 1975). In contrast, patients with AD have extremely low cortisol levels before their morning dose of hydrocortisone (with lower than normal levels between midnight and the early hours of the morning); after taking the medication, however, cortisol levels increase rapidly (Burke, 1985). Hence, while healthy individuals secrete cortisol in a steady pulsatile fashion, patients with AD experience fluctuating levels.

This variability could play an important role in the cognitive functioning of patients with AD. The relationship between cognition and circulating glucocorticoids typically follows an inverted-U shaped pattern. Specifically, a certain level of cortisol is needed to enhance cognitive functioning; decreases below or increases beyond the threshold of optimal functioning impair cognition (Conrad et al., 1999; McEwen, 1997). Hence, the irregular rhythm of cortisol secretion in patients with AD, and its relationship to their cognitive functioning, merits investigation.

Only a few published studies have reported on objective measures of cognitive functioning in patients with AD. Klement et al. (2010; 2009) found significant differences between patients with AD and healthy controls on tests of selective attention and verbal memory. There are two notes of import here, however. First, these cognitive tests were administered during experiments designed to test the effects of glucose administration on cognitive functioning in patients with AD, and so the researchers did not administer a comprehensive battery assessing performance in a variety of cognitive domains under ordinary conditions. Second, the memory test was not one administered commonly in the clinic, and had no

established psychometric properties. Third, the memory test did not require delayed recall of the word lists; therefore, it was not possible to measure how effectively patients retained information across time.

Specific Aims and Hypotheses

Patients with AD frequently present with memory and attention complaints, despite being on replacement therapy. Very few studies have, however, provided in-depth examination of memory and attention (and of other cognitive domains) in patients with AD, comparing their performance to that of individuals free of any chronic illness.

Hence, the present study aimed to quantify and describe the functioning of patients with AD across a variety of cognitive domains, and to compare their cognitive function to that of healthy controls. Our working hypothesis was that, compared to healthy controls, patients with AD would score more poorly on tests of memory and attention, but that their performance would be relatively intact on measures of other cognitive functions.

Under optimal conditions, neuropsychological assessment includes an in-person, face-to-face administration of a battery of standardized tests designed to measure functioning in various cognitive domains (Lezak, Howieson, & Loring, 2004). Such formal administration is obligatory (or, at least, highly desirable) in the context of forensic evaluations, or in particular clinical and research circumstances. In some situations, however, in-person, face-to-face administration is impractical or impracticable. For instance, in resource-limited settings, such as those one might encounter in low- or middle-income countries (LAMICs), large-scale research studies might have to use alternative means of test administration in order to increase sample size in a cost-efficient manner, and to reduce the sampling bias that might arise from excluding participants who are unable, unwilling, or not healthy enough to travel to the study site (Dura & Kiecolt-

Glaser, 1990; Lavrakas, 1993). Using such alternative means of test administration becomes even more of an imperative when researchers in low-resource settings are studying disorders or illnesses with a low base rate of diagnosis in the population. Performing a formal, comprehensive, face-to-face neuropsychological assessment is not feasible when patients (a) are few in number, (b) are scattered geographically, and (c) suffer from a medical condition that might prevent extended testing sessions.

Telephone assessment of cognitive functioning provides a viable alternative in circumstances such as these. Advances in telecommunications technology, along with the fact that most individuals, even in LAMICs, have access to a personal handset, make telephone-based data collection increasingly attractive (Donner, Gitau, & Marsden, 2011; Kempf & Remington, 2007; Swanepoel & Thomas, 2012). Hence, researchers have developed numerous telephone cognitive assessment batteries. Many of these serve as brief screening tools for dementia and other neurodegenerative diseases, or as a means to track changes in cognitive function longitudinally; most can detect, reliably and with good validity, the presence or absence of gross cognitive deficits (Crooks, Clark, Petitti, Chui, & Chiu, 2005; Dombovy, Drew-Cates, & Serdars, 1998; Duff, Beglinger, & Adams, 2009; Gallo & Breitner, 1995; Guerini et al., 2008).

In the current study, we used the Brief Test of Adult Cognition by Telephone (BTACT; Lachman & Tun, 2008; Tun & Lachman, 2005) to assess cognitive functioning in patients with AD who lived in various provinces of South Africa. The BTACT is a psychometrically sound instrument that, unlike many other telephone cognitive batteries, assesses a wide range of cognitive abilities; therefore, it can be used for multiple clinical purposes and in many different clinical populations (Gavett, Crane, & Dams-O'Connor, 2013; Tun & Lachman, 2006). It has, for

instance, been used successfully in large-scale research measuring global cognition in young, middle-aged, and older adults (Brim, Ryff, & Kessler, 2004; Gurnani, John, & Gavett, 2013).

Methods

Participants

This study is part of a larger research programme investigating quality of life in AD. To support that programme, patients are recruited from the South African Addison's Disease Database (SAAD; Ross et al., 2010), and healthy controls are recruited using flyers and posters placed on notice boards around the university community and in the offices of large corporations in the Cape Town metropole.

This study featured a case-control design in which we selected participants to form two matched groups: 35 adult patients with AD, and 35 community-dwelling volunteers who were free of any chronic illness.⁶ We matched the groups on age (AD: $M = 51.09$ years, $SD = 14.81$, range = 20-72; controls: $M = 50.89$ years, $SD = 14.58$, range = 21-74; between-group comparison, $t(68) = -0.057$, $p = .955$), education (AD: $M = 13.61$ years, $SD = 2.26$, range = 8-17; controls: $M = 14.43$ years, $SD = 2.89$, range = 10-21; between-group comparison, $t(66) = 1.30$, $p = .198$), sex distribution (9 males and 26 females in each group), and race distribution (30 white and 5 coloured individuals in the control group, and 32 white and 3 coloured individuals in the AD group).

Ethical Considerations

The research ethics committees of the University of Cape Town's Department of Psychology and Faculty of Health Sciences approved the study procedures.

⁶Initially, we contacted 43 patients with AD and asked whether they would be willing to participate. Three indicated such willingness, but then did not respond to repeated telephone calls. Another five declined participation.

Subjects were invited participate in this study and if they agreed, were asked to give their verbal consent. The purpose of the study was explained to all participants, what was expected of them, and that their confidentiality would be ensured and maintained. All participants had the freedom to withdraw their participation at any point. For patients with AD, whether or not they chose to participate in this study had no influence on their current treatment from their treating endocrinologist or doctor.

There were no risks associated with the telephonic cognitive assessment administered, however if participants felt uncomfortable with any of the questions they were free to withdraw from the study at any time. Participants were made aware that there were no financial benefits from participating in this study.

Materials

Sociodemographic questionnaire (see Appendices C and D). This instrument captured specific information from participants regarding (a) demographic variables (e.g., age, race), (b) their medical history, and, for patients with AD, (c) type, dosage, and timing of current medication, and length of time since diagnosis.

Beck Depression Inventory-Second Edition (BDI-II). Patients with AD frequently present with disturbances in mood, motivation, and behavior (Ten et al., 2001). Hence, we used this 21-item self-report instrument (Beck et al., 1996) to measure the intensity, severity, and depth of depression in respondents.

Brief Test of Adult Cognition by Telephone. The BTACT (Tun & Lachman, 2006) is a brief (15-minute) test of cognition that can be administered over the telephone. It consists of subtests that measure episodic memory, working memory, executive functioning, reasoning, and speed of processing. Although there are no test manuals or published articles detailing the formal

psychometric properties (e.g., convergent and divergent validity) of the instrument, the BTACT's developers do report that their telephonic assessment correlates well with a face-to-face administration of the same test battery (r ranging from .56 – .95), and that it possesses good test-retest reliability (r reaching up to .87).

The first BTACT subtest assesses *episodic memory* using the word list from the Rey Auditory-Verbal Learning Test (RAVLT; Lezak et al., 2004). Participants are read a list of 15 words and are then asked to recall as many as possible; this is the Immediate Recall trial. At the end of the assessment session, the participant is again asked to recall as many words as possible from the list; this is the Delayed Recall trial.

The rest of the BTACT subtests are administered, in the order given below, inbetween the episodic memory Immediate Recall and Delayed Recall trials. *Working memory* is assessed using the Digit Span-Backwards subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1997a). Participants are read increasingly longer sequences of randomly-ordered digits (from a string of two to a string of eight) and asked to repeat them back in reverse order. The test is discontinued when an examinee fails both trials at a particular sequence length.

The BTACT assesses *executive* functioning using a Category Fluency task. Participants are asked to generate as many words as possible, in one minute, from a particular semantic category (in this case, *animals*; Lezak et al., 2004).

The next subtest, Red-Green, assesses *attention-switching/reaction time* using a series of three simple two-choice response tasks. In the baseline task, participants are instructed to respond “go” when they hear the word *green*, and “stop” when they hear the word *red*. After completing 20 such trials, the examiner begins administration of the reverse baseline task. Here, the participant is instructed to make the opposite responses: “go” to red and “stop” to green.

After completing 20 such trials, the examiner begins administration of the alternating task. Here, the participant is given cues as to when to use the response rule corresponding to the baseline task, and when to use that corresponding to the reverse baseline task. The examiner administers 32 such trials. The baseline tasks assess processing speed, and the alternating task assesses task-switching and inhibitory control.

The next subtest, Number Series, assesses *reasoning*. Participants are read five different series of five numbers each, and asked which number they think best continues each sequence (Schaie, 1996). Finally, the Counting Backwards subtest assesses *speed of processing* by asking participants to count backwards from 100 as quickly and accurately as possible for 30 seconds.

Procedure

All participants provided written informed consent as part of the larger research programme in which they were enrolled. I contacted potential participants telephonically and asked whether they were willing to enrol in the study. Those who provided verbal consent were given an appointment date and time, and were told that a study representative would telephone them at that time to administer the cognitive tests. Patients with AD were asked when they took their morning medication; the appointment time was scheduled for 2 hours later than that. By building in this 2-hour time gap, we sought to ensure that testing took place after the initial effects of the medication had subsided (i.e., after the sharp peak that follows hydrocortisone administration; Groves et al., 1988; Løvås & Husebye, 2007), but before cortisol levels dropped so low that cognitive performance might be affected (Rimmele, Meier, Lange, & Born, 2010).

At the appointed time, I telephoned the participant and administered the BTACT following the standard procedures detailed by Tun and Lachman (2005; 2006). She obtained verbal consent again, and assured participants of the confidentiality of their responses and their

data. Participants were also told that if at any time during the test they wanted to stop they could, or if they felt uncomfortable doing a subtest they should say so and the administrator would move on to the next subtest. Furthermore, the test administrator emphasized that participants should not write anything down, and should do everything mentally.

We tested each patient with his/her matched control at the same time of day.

Data Management and Statistical Analyses

Scoring the BTACT and deriving outcome variables. We scored the BTACT, and derived a set of outcome variables from it, using the standard procedures detailed by Tun and Lachman (2005; 2006). Specifically, for the episodic memory subtest we scored the Immediate Recall trial by assigning one point to each word recalled correctly; we scored the Delayed Recall trial identically. We then calculated, as a measure of forgetting: the difference between the Immediate and Delayed Recall scores. We also recorded the number of false alarms (i.e., the number of times a participant produced a word that was not on the original list) on both recall trials.

For the Category Fluency subtest, the outcome was the number of unique words generated within the 1-min time limit. For the Digit Span-Backwards subtest, the outcome was the largest correct set size (out of a possible 8). For the Red-Green subtest, the outcome variables were derived from the alternating task: the number of correct responses made (out of a possible 32) and the time to complete the set of 32 trials. For the Number Series subtest, the outcome was the number of series completed correctly (out of a possible 5). Finally, for the Counting Backwards subtest, the outcome was the total number of digits counted backwards in the correct order within the time limit. The number of errors made was subtracted from this outcome score

to produce a final score (e.g., if a participant counted 30 numbers backwards in the correct order but made 4 errors, their total score would have been 26 numbers).

A BTACT composite score was calculated by taking the average of standardised z-scores for 5 of the 6 BTACT subtests: AVLT (the total of the Immediate and Delayed total scores combined), Category Fluency, DS-Backwards, Number Series, and Counting Backwards (Tun & Lachman, 2006).

We also scored the BTACT using the Bi-factor scoring method described by Gavett and colleagues (2013). By and large, the results associated with analyses of those scores were consistent with those from the standard scoring method (see Appendix E).

Power analysis and sample selection. A power analysis suggested that the sample size be set at $N = 88$ (44 per group) to achieve a power of .75, given a medium effect size (Cohen's $d = 0.50$ and an alpha of .05; Erdfelder, Faul, & Buchner, 1996). However, given the rarity of AD, only 35 patients (and hence $N = 70$) could be enrolled. This sample size generated statistical power of .66.

Inferential analyses. We completed all analyses using SPSS (Version 22) and R (the `Exact` package). We set the threshold for statistical significance (α) at .05, unless otherwise noted. For each of the analyses described below, we calculated the appropriate effect size estimate, and we interpreted these estimates following convention (e.g., for Cohen's d , 0.20-0.30 = small; 0.50 = medium; > 0.80 = large). Where assumptions underlying inferential statistical tests were violated, appropriate non-parametric tests were used and noted in the results section below.

The analyses proceeded across four stages. First, we used a series of independent-sample t -tests to compare group performance on each BTACT outcome variable. A Bonferroni

correction controlled for inflated familywise error associated with multiple pairwise comparisons; in this case, the adjusted threshold for statistical significance is $\alpha = .05 / 12 = .004$. Second, we used bivariate correlational analyses (with Pearson's r coefficient) and Fischer's Exact Tests (for categorical variables) to assess whether, in each group separately, demographic characteristics (i.e., age, sex, education, income, and depression) influenced cognitive performance. Third, we used bivariate correlational analyses (with Pearson's r coefficient) to assess whether, in the AD group, disease characteristics (i.e., time since diagnosis, total hydrocortisone dose, dose/kg, and number of doses/day) influenced cognitive performance. Fourth, a series of Fisher's Exact Tests sought to determine whether, in the AD group, there was an association between timing of the last dose (before noon, $n = 8$; between noon and 18h00, $n = 14$; after 18h00, $n = 13$) and cognitive performance.

Results

Table 4 presents the clinical characteristics of the group of patients with AD. Of note here is that 4 participants (two women, aged 46 and 50 years, and two men aged 38 and 60 years) were not prescribed hydrocortisone; instead, they were prescribed prednisone. The average prednisone dose was 8.13mg ($SD = 4.73$), and the average prednisone/kg ratio was 0.09 mg/kg ($SD = 0.04$).

Table 4

Clinical Characteristics of Patients with Addison's Disease (N = 35)

	<i>M (SD)</i>	Range
Age at diagnosis (years)	32.80 (15.50)	4 - 65
Duration of AD (years)	18.29 (11.75)	1 - 50
Total hydrocortisone dose	22.50 (6.79) ^a	10 - 35
Hydrocortisone/kg	0.33 (0.14) ^a	0.13 – 0.70
Number of doses per day	2.03 (0.71)	1 - 3
Concurrent co-morbid diseases	1.66 (1.80)	0 - 7

^aData based on 30 participants (1 patient did not provide information on their hydrocortisone dosage, and 4 were prescribed prednisone).

Table 5 presents between-group comparisons of demographic variables. There were no statistically significant between-group differences for age ($p = .955$), education ($p = .198$), or BMI ($p = .591$). There was however a statistically significant between-group difference for (a) income ($p = .015$), with a larger proportion of control participants having a higher income, and (b) depression ($p = .009$), patients with AD had significantly higher levels of depression.

Table 6 presents between-group comparisons of BTACT performance. At the conventional level of significance, patients with AD performed significantly more poorly than controls on a number of outcome variables related to episodic memory performance (number of false alarms on both the Immediate and Delayed Recall trials; Delayed Recall; amount of information lost over the delay (Immediate – Delayed score), working memory, speed of processing, and overall cognitive functioning (Composite z-score). After the Bonferroni correction, only three between-group differences remained significant: (1) In patients with AD, the difference between the number of words produced on both the Immediate and Delayed Recall trials of the episodic memory subtest was significantly larger than that for controls (see Figure

8), and patients with AD made significantly more false alarms on the AVLT immediate and delayed recall trials compared to controls.⁷

Table 5
Comparison of Group Demographic Variables (N = 70)

Variable	Group		t / χ^2	p	ESE
	AD ($n = 35$)	Controls ($n = 35$)			
Age	51.09 (14.81)	50.89 (14.58)	0.06	.955	0.01
Education	13.61 (2.26)	14.43 (2.89)	1.30	.198	0.32
Body mass index**	26.43 (5.67) ^b	25.35 (3.85) ^d	487.00	.591	0.07
Income (in ZAR) ^a			- ^e	.015*	0.44
1000-2499	3	0			
2500-5499	5	4			
5500-9999	7	0			
10000-19999	6	11			
20000-30000	3	4			
> 30000	9	15			
BDI-II	11.94 (9.93) ^c	6.34 (7.18)	-2.69	.009*	

Note. For all variables, means are presented with standard deviations in parentheses, except for the variable Income, where actual counts are presented.

^aData based on 33 patients in the AD group and 34 participants in the control group (2 patients with AD and 1 control participant chose not to specify their income).

^bData based on 32 participants (2 patients did not provide information about their height, and 1 patient did not provide information about both their height or weight).

^cData based on 34 patients (1 patient omitted one question in the BDI).

^dData based on 33 participants (2 participants did not provide information about both their height or weight).

^eFischer's Exact test performed therefore no test statistic was calculated.

* $p < .05$.

** Mann Whitney U test performed. In this case, test statistic = U , effect size = r .

⁷This pattern of results remained consistent when we removed from the analysis the four patients with AD who were prescribed prednisone. Hence, the variability in half-life between hydrocortisone and prednisone appears to have few effects on the pattern of cognitive performance observed in patients with AD.

Table 6
Comparison of Group Performance on the BTACT (N = 70)

Variable	Group		<i>t</i>	<i>p</i>	ESE
	AD (<i>n</i> = 35)	Controls (<i>n</i> = 35)			
Episodic memory					
Immediate Recall	6.06 (2.85)	6.74 (2.50)	1.07	.144	0.25
Delayed Recall	3.46 (3.03)	5.29 (2.99)	2.54	.007*	0.61
Immediate – Delayed	2.60 (1.77)	1.46 (1.36)	-3.03	.002**	0.72
False alarms (Immediate)***	0.31 (0.47)	0 (0)	420.00	<.001**	0.43
False alarms (Delayed)***	0.54 (0.85)	0.09 (0.37)	406.00	<.001**	0.40
Working memory					
Digit Span-Backwards	4.54 (1.50)	5.14 (1.38)	1.74	.043*	0.42
Executive functioning					
Category Fluency	15.26 (3.86)	16.26 (5.20)	0.91	.182	0.22
Red-Green (total score)	30.79 (2.44) ^a	31.47 (0.86) ^c	1.53	.065	0.37
Reasoning					
Number Series	2.14 (1.63)	2.40 (1.83)	0.62	.269	0.15
Speed of processing					
Counting Backwards	31.74 (11.42)	36.97 (8.92)	2.14	.018*	0.51
Red-Green (completion time) ^a	79.66 (15.72) ^b	69.62 (13.51) ^c	-2.79	.004*	0.69
Composite z-score	-0.18 (0.76)	0.15 (0.64)	2.02	.024*	0.47

Note. Means are presented with standard deviations in parentheses. BTACT = Brief Test of Adult Cognition by Telephone; AD = Addison's disease; ESE = effect size estimate (in this case, Cohen's *d*).

^aData based on 33 participants (2 participants from the AD group, a 55-year-old female and 68-year-old female, requested this subtest be stopped as they were struggling).

^bData based on 32 participants (the 2 participants in the AD group who requested this subtest be stopped did not have a completion time, and 1 participant from the AD group, 72-year-old female's completion time was not recorded due to a technical error on the researcher's part).

^cData based on 34 participants (1 participant from the control group, a 28-year-old female, was not administered this subtest due to a technical error on the researcher's part).

p* < .05. *p* < .004 (i.e., statistically significant after a Bonferroni correction).

***Mann Whitney *U* test performed. In this case, test statistic = *U*, effect size = *r*.

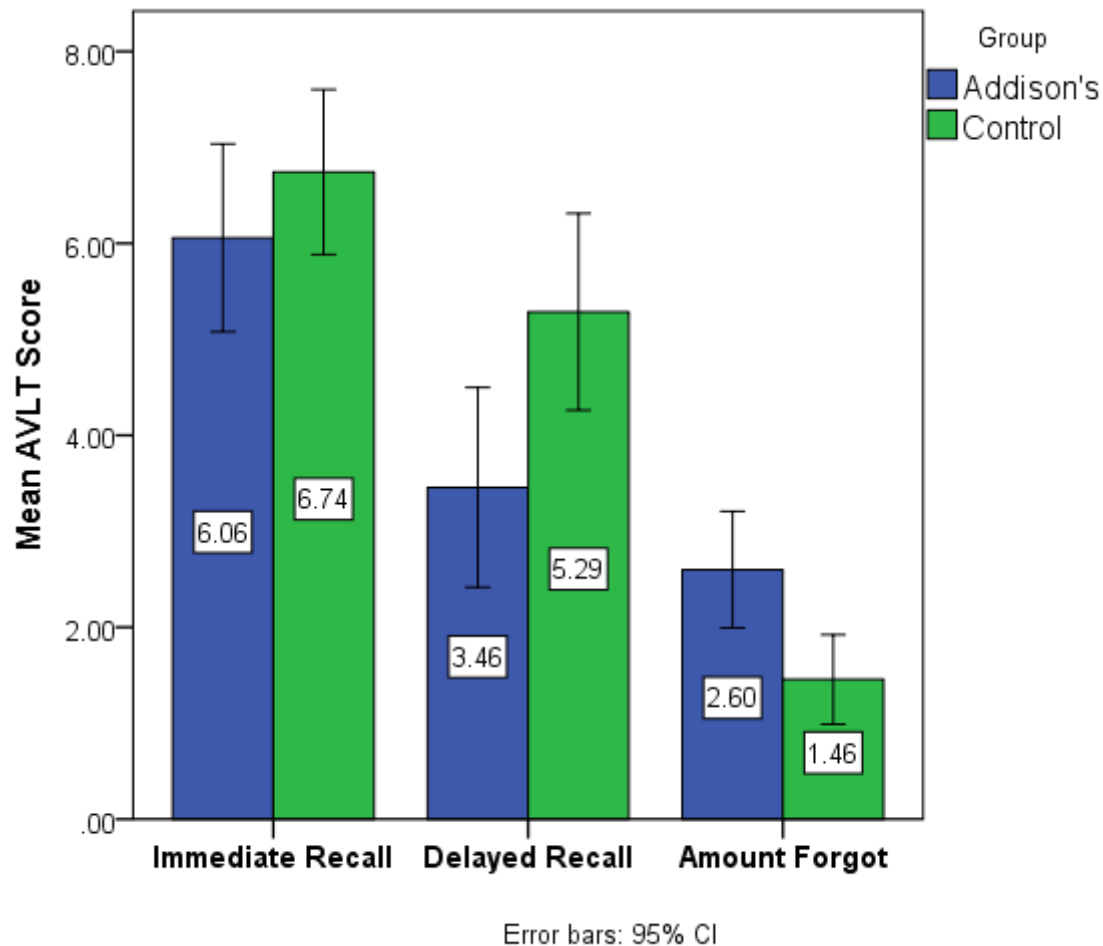


Figure 8. AVLT performance between patients with AD and controls.

Associations between Demographic and Cognitive Variables

Within each group, we calculated associations between demographic (age, education, gender, income, and BDI-II (depression)) variables and each of the BTACT outcome variables. For the continuous variables age, education, and BDI-II, we performed Pearson's r correlations, and for the categorical variable gender we performed Fischer's Exact tests (because >20% cell counts were less than 5).

Within the AD group, the analyses detected (i) a positive association between age and number of False Alarms produced at immediate recall on the AVLT ($r = .36, p = .017$), and (ii) negative associations between age and (a) working memory ($r = -.45, p = .005$), (b) Category

Fluency ($r = -.43, p = .005$), (c) Counting Backwards ($r = -.47, p = .002$), and (d) Conventional z-score ($r = -.50, p = .001$). All of these associations suggest that patients of an older age performed more poorly.

The analyses detected positive associations between education and (a) delayed recall on the AVLTL ($r = .45, p = .004$), (b) working memory ($r = .36, p = .020$), (c) Category Fluency ($r = .51, p = .001$), (d) Reasoning ($r = .39, p = .013$), (e) Counting Backwards ($r = .43, p = .006$), and (f) Composite z-score ($r = .52, p = .001$). All of these associations suggest that patients with a higher education level performed better. The analyses detected no associations between BDI-II scores and BTACT variables. A series of Fisher's Exact Tests sought to determine whether, in the AD group, there was an association between sex (female, $n = 26$; male, $n = 9$) and BTACT outcome variable scores. The analyses detected no significant associations, all $ps > .064$, Cramer's $Vs < 1.00$.

Within the control group, the analyses detected (i) positive associations between age and difference between number of words produced on the immediate and delayed recall on the AVLTL ($r = .34, p = .022$), and (ii) negative associations between age and (a) delayed recall on the AVLTL ($r = -.34, p = .024$), and (b) Counting Backwards ($r = -.39, p = .011$). All of these associations suggest that controls of an older age performed more poorly. The analyses detected no associations between BTACT outcome variables scores and either (a) education levels, or (b) BDI-II scores.

A series of Fisher's Exact Tests sought to determine whether, in the control group, there was an association between sex (female, $n = 26$; male, $n = 9$) and BTACT outcome variable scores. The analyses detected no significant associations, all $ps > .153$, Cramer's $Vs < 1.00$.

Associations between Disease Characteristics and Cognitive Variables

Table 7 presents the results of correlational analyses investigating associations between disease characteristics and cognitive performance. Neither total hydrocortisone dose, dosage/kg nor number of doses per day correlated significantly with performance on any of the subtests. However, duration of illness correlated significantly with Red-Green (completion time). The direction of these correlations indicates that patients who had AD for a longer period of time had a slower speed of processing. Age at diagnosis correlated significantly with several indicators of episodic memory performance: number of words produced at Immediate and Delayed Recall, and number of False Alarms produced at Immediate Recall. Age at diagnosis also correlated significantly with Digit Span-Backwards, Counting Backwards, and the composite z-score. The order of these correlations indicated that patients who were diagnosed later in life had poorer declarative and working memory, and a slower speed of processing, and an overall greater cognitive impairment.

A series of Fisher's Exact Tests sought to determine whether, in the AD group, there was an association between timing of the last dose (before noon, $n = 8$; between noon and 18h00, $n = 11$; after 18h00, $n = 16$) and BTACT outcome variable scores. The analyses detected no significant associations, all $ps > .086$, Cramer's $Vs < 1.00$.

Table 7

Correlation of BTACT Measures with Addison's Disease Clinical Characteristics

	Age at diagnosis	Time since diagnosis	Total HC dose ^c	HC/kg ^c	Number of doses/day
Episodic memory					
Immediate Recall	-0.29* (.049)	-0.03	-0.11	-0.11	0.15
Delayed Recall	-0.29* (.044)	0.01	-0.14	-0.11	0.21
Immediate – Delayed	0.04	-0.06	0.02	0.02	-0.13
False alarms (Immediate)	0.30* (.026)	0.02	0.13	0.11	0.06
False alarms (Delayed)	0.02	0.02	-0.17	-0.17	-0.03
Working memory					
Digit Span-Backwards	-0.32* (.032)	-0.13	0.09	0.09	0.01
Executive functioning					
Category Fluency	-0.20	-0.28	0.04	0.04	0.22
Red-Green (total score) ^a	-0.07	-0.27	0.23	0.23	0.23
Reasoning					
Number Series	-0.16	-0.20	-0.08	-0.09	0.10
Speed of processing					
Counting Backwards	-0.40* (.008)	-0.06	0.19	0.19	0.15
Red-Green (completion time) ^b	0.02	0.39* (.014)	-0.12	-0.12	0.08
Composite z-score	-0.36* (.018)	-0.17	0.02	0.12	0.16

Note. Statistic presented is Pearson's r correlation coefficient. p -values are presented in parentheses for statistically significant correlations. HC = hydrocortisone.

^aData based on 33 participants (2 patients, a 55-year-old female and 68-year-old female, requested this subtest be stopped as they were struggling).

^bData based on 32 participants (the 2 patients in the AD group who requested this subtest be stopped did not have a completion time, and 1 patient from the AD group, 72-year-old female's completion time was not recorded due to a technical error on the researchers' part).

^cData based on 30 participants (1 patient did not provide information on their hydrocortisone dosage, and 4 were prescribed prednisone).

* $p < .05$.

We ran a set of secondary analyses to determine whether the character of certain comorbid illnesses in the AD group influenced their cognitive functioning. In the patient group, the most common comorbid illnesses were hypothyroidism (22.9%, 8 people), diabetes mellitus (22.9%, 8 people), hypertension (14.3 %, 5 people), osteoporosis (11.4%, 4 people), high cholesterol (11.4%, 4 people), asthma (8.6%, 3 people), fibromyalgia (5.7%, 2 people), depression (5.7%, 2 people), arthritis (5.7%, 2 people), high blood pressure (5.7%, 2 people), and Autoimmune Polysyndromes Type II (5.7%, 2 people). Two separate independent samples *t*-test compared BTACT performance in patients who had diabetes mellitus versus those who did not, and in patients who had hypothyroidism versus those who did not. There were no significant between-group differences on any of the outcome variables in the diabetes analysis ($ps > .06$). However, when comparing patients who had hypothyroidism versus those who did not, two statistically significant between-group differences arose: (a) Number of false alarms produced on the AVLIT immediate recall (patients with hypothyroidism: $M = 0$, $SD = 0$; patients without hypothyroidism: $M = 0.41$, $SD = 0.50$; between-group comparison, $t(26) = 4.23$, $p < .001$), (b) Number of words spontaneously produced in the Category Fluency task (patients with hypothyroidism: $M = 18.00$, $SD = 3.63$; patients without hypothyroidism: $M = 14.44$, $SD = 3.60$; between-group comparison, $t(33) = -2.45$, $p = .020$). Hence, in this limited sample, it does not appear that the character of comorbid illness has a major impact on cognitive functioning in patients with AD.

Discussion

We used the Brief Test of Adult Cognition by Telephone (Lachman & Tun, 2008; Tun & Lachman, 2005) to assess cognitive functioning in a sample of patients with AD from South Africa. Confirming our working hypothesis, patients with AD showed, relative to

demographically-matched healthy controls, significantly impaired verbal declarative memory (associated with medium-to-large effect sizes). No other domains of cognition appeared impaired in the AD group; hence, the working hypothesis that patients with AD would show impaired attentional functioning (which would have been tapped by the working memory and executive functioning subtests of the BTACT) was not confirmed.

Regarding our statistical analyses, we used the Bonferroni correction to control for the use of multiple *t*-tests and to therefore avoid Type I errors (i.e., incorrectly reporting that a relationship exists between two variables). However, such corrections increase the likelihood of Type II errors (incorrectly dismissing a relationship between two variables). In public health research, it is important not to miss real effects, which would mean underestimating a real health risk (Jacobson & Jacobson, 2005). Hence, the current study's context might mean that taking the Bonferroni correction is too strict: There should be concern over making Type II, rather Type I, errors. In light of this consideration, perhaps the AD groups' performance on the working memory and speed of processing tests should be evaluated at the conventional threshold for statistical significance ($p < .05$), and perhaps one might seek clinical significance in that finding.

Regardless of these statistical considerations around types of error, episodic memory remains clearly the domain of greatest impairment in this sample of patients with AD. Profound fluctuations in glucocorticoids that underlie many of the manifestations of AD are likely to contribute to impaired memory performance. Glucocorticoids have multiple effects on the human central nervous system, but have particularly dramatic effects on the hippocampus, a brain region critical for new learning and memory (Kim & Diamond, 2002; Squire, 1992). More specifically, a cortisol deficiency such as that seen in AD may result in cell death in the hippocampus and PFC, resulting in memory impairment.

However, most patients with AD are supplemented with hydrocortisone, meaning they do not experience chronic cortisol deficiencies and may even have supraphysiological levels of the hormone. Increased levels of glucocorticoids reduce hippocampal glucose uptake (De Leon et al., 1997) and neuronal excitability (Joëls, 2001), impair synaptic plasticity (Diamond, Bennett, Fleshner, & Rose, 1992; Pavlides, Ogawa, Kimura, & McEwen, 1996), decrease the number of newly-generated neurons, and alter synaptic density in the CA1 and CA3 regions of the structure (Shors, Chua, & Falduto, 2001). Prolonged levels of increased glucocorticoids (such as continuously taking hydrocortisone medication) may produce permanent degeneration of hippocampal neurons and atrophy of dendrites in the CA3 region of the hippocampus (Sapolsky et al., 1986).

The brain-based effects of glucocorticoids are not limited to the hippocampus, of course: Cortisol secretion enhances dopaminergic activity and increases glutamate levels in the PFC, and also alters dendritic organization in that structure (Arnsten & Pliszka, 2011; Moghaddam, 2002). This brain structure plays an important role in declarative memory retrieval, particularly in post-retrieval monitoring processes. More specifically, during post-retrieval monitoring the PFC is involved in search and decision-making processes necessary to determine whether an event occurred in a specific context (Burgess, 1996), thereby allowing the accurate reconstruction of memories.

The effects of cortisol on the hippocampus and PFC can affect memory processes because both of those regions play integral roles in memory processing, and both have dense concentrations of glucocorticoid receptors (Alderson & Novack, 2002; Kim & Diamond, 2002; Schacter & Wagner, 1999; Shansky & Lipps, 2013). Consequently, researchers hypothesize that increases in glucocorticoid levels can impair contextual and declarative memory tasks that are

known to require hippocampal and PFC function (Arnsten, 2009; De Quervain et al., 2003; Payne, Elie, Blackwell, & Neuschatz, 1996). These hypotheses have been confirmed by numerous studies showing that contextual and declarative memory tasks are particularly impaired by exposure to environmental stressors (Lupien et al., 1997).

The memory deficits seen in patients with AD could also be explained by differential activation of brain receptors. Most of these effects of cortisol on the human hippocampus and PFC are mediated by the interaction of glucocorticoids with MRs and GRs (Wolf, 2003). MRs bind naturally circulating cortisol with high affinity; they are involved in behavioural reactivity to novel situations necessary to encode new information. In contrast, GRs have a lower affinity for cortisol and only become heavily occupied after a stressor or an event that raises cortisol levels (Wolf, 2003); they are involved in consolidation and retrieval of learned information (de Kloet et al., 1999; Kirschbaum et al., 1996). In support of the assertion that a balanced activation of receptors is needed for optimum memory performance, Tytherleigh et al. (2004) found that adequately treated patients with AD performed significantly better on a declarative memory recall and working memory tasks when both receptor types were activated compared to when only either MRs or GRs were activated. These results suggest that a balanced activation of both receptors may be needed for optimal memory functioning in humans. Research in healthy controls has corroborated this notion. For example, de Kloet et al. (1999) showed that activation of both MRs and GRs are a prerequisite for optimal memory functioning.

The data we report here are not entirely consistent with previous research investigating cognitive function in patients with AD. For instance, Klement et al. (2010; 2009) found, using the Stroop test, significantly impaired attentional functioning in their AD group; in contrast, we found no deficits on those BTACT subtests that might tap into attentional functioning (i.e., the

tests of working memory and executive functioning). In this case, the disparity in findings across studies might be attributable to the use of different (and, one might argue, deficient) measures of an exceptionally broad cognitive construct.

Klement et al. (2010; 2009) also found that their AD group performed significantly more poorly than controls on immediate recall of a 30-item word list. In contrast, we found no significant between-group differences on the immediate recall trial of the BTACT episodic memory subtest. Of particular interest here, perhaps, is that by the delayed recall trial our AD group had forgotten significantly more words than had the healthy controls. This pattern of data might be explained as follows: On the immediate recall trial, it is possible that patients recalled words relying solely on their working memory systems (and our results suggest that working memory was not impaired in our sample of patients). However, on the delayed recall trial, participants would need effortful retrieval strategies (requiring intact functioning of the PFC) to recall previously-learned information. As we have discussed above, abnormal cortisol levels may not allow for such efficient use of such retrieval strategies.

Age at diagnosis was an important predictor of performance on several BTACT subtests. Specifically, patients diagnosed later in life performed more poorly on tests of episodic and working memory, speed of processing, and had poorer overall cognition. Since cognitive functioning is known to decline with age (Leiva, Andrés, Servera, Verbruggen, & Parmentier, 2016; Meusel et al., 2017; Salthouse, 1996; Verhaeghen & Salthouse, 1997), and increased cortisol levels impair cognition (taking hydrocortisone medication is known to cause periods of sub-and-supra physiological cortisol levels), perhaps older people are more susceptible to the impact of altered cortisol on brain structures required for successful cognitive functioning within those particular domains.

Moreover, longer disease duration was associated with slower processing speed. Again, this finding may be related to age since longer disease duration implies increased age, and processing speed has been shown to decline with age (Eckert, 2011). Of note is that neither total hydrocortisone dose nor dosage/kg was not a significant predictor of cognitive functioning. In this sample, however, the distribution of dosage/kg values had a small standard deviation, and hence there was perhaps not enough of a range to detect dosage effects on cognition.

In terms of demographic variables influence on cognition, age played an important role. Across both the AD and control group, older age was associated with worse memory performance and a slower speed of processing. Given that cognitive functioning is known to decline with age (Leiva et al., 2016; Meusel et al., 2017; Salthouse, 1996; Verhaeghen & Salthouse, 1997) this result is not surprising. Within the AD group, higher level of education was associated with better cognitive functioning. This result is not surprising, since performance on a variety of neuropsychological tests is influenced by level of education (Strauss, Sherman, & Spreen, 2006; Van Hooren et al., 2007). This result was not replicated in the control group, perhaps due to the higher and more homogenous education levels within this group. Neither gender nor depression levels seemed to impact cognitive functioning.

Limitations

We interpret all of our data while acknowledging that this study had several limitations. First, the relatively small sample size (a consequence of rarity of AD) meant that our statistical analyses were slightly underpowered ($1 - \beta = .66$). Second, although the BTACT was tolerated well and proved useful in helping us test a socioeconomically and geographically diverse group of patients, the instrument is not immune to the same criticism that faces other telephone test batteries. Specifically, well-documented limitations of telephone cognitive assessment are that

(a) the impossibility of presenting visual stimuli over the telephone means that important aspects of cognitive functioning cannot be assessed, and (b) the brevity of such batteries means that they do not include sufficient items to sample the wide range of abilities typically assessed in an in-person, face-to-face neuropsychological assessment (Crooks, Petitti, Robins, & Buckwalter, 2006; Duff et al., 2009). Third, it would be of interest to measure cortisol levels in patients with AD and correlate these with cognitive functioning. By design, we assumed that when we telephoned patients they were in a physiological state where cortisol levels were neither too high nor too low (therefore providing an optimal level of functioning); we have no objective evidence to verify that assumption, however. It would also be of interest to test cognitive functioning at various time intervals after medication doses are taken to determine at what stage optimal cognitive functioning occurs in these patients. Data from such a study might prove useful in determining individual differences in what level of cortisol is needed for optimal cognitive functioning, and at what point cortisol levels begin to hinder cognition. Finally, we did not collect data on the presence of acute illness at the time of testing, or on the presence of sleep disruptions the night before testing. Such variables might have a negative impact on cognitive functioning; future studies should attempt to capture data on them, and consider their potential as confounders.

Conclusions

In conclusion, we showed that patients with AD perform more poorly on tests of episodic memory (particularly at the delayed recall stage) than demographically-matched healthy controls. These results are not confounded by between-group differences in level of education, or by differences in the type of medication prescribed to the AD patients. We also showed that the BTACT could be used successfully to discriminate between the cognitive performance of

patients with AD and healthy controls. Although this latter result is promising in that it shows how successfully alternative means of assessment might be adopted in a resource-limited setting, we do acknowledge that studies featuring more comprehensive neuropsychological assessment are needed to fully explore the deficits in memory performance in patients with AD. For instance, at present the literature documents only deficits in verbal declarative memory, but that might be solely because non-verbal/spatial memory has not been investigated. If alterations in cortisol secretion affect hippocampally-dependent memory, there is no reason to suspect that the effect should be material-specific; that is, there should be both verbal and spatial memory deficits (Luine et al., 1994; Schwabe, Dalm, Schächinger, & Oitzl, 2008). Furthermore, no studies have investigated non-declarative or procedural forms of memory (e.g., perceptual and conceptual priming) in patients with AD. Describing the full extent and nature of the memory deficits in AD is an important step toward being able to ascertain the mechanisms underlying such impairment.

CHAPTER FIVE

STUDY 3 - Impaired Quality and Efficiency of Sleep Impairs Cognitive Functioning in Addison's Disease

A version of this chapter has been published as a peer-reviewed journal article:

Henry, M., Ross, I.L., Wolf, P.S.A., & Thomas, K.G.F. (2017). Impaired quality and efficiency of sleep impairs cognitive functioning in Addison's disease. *Psychoneuroendocrinology*, 78, 237-245. DOI: 10.1016/j.psyneuen.2017.02.004.

This chapter differs from the original article in that here I have: (1) added analyses of data from a declarative memory test not reported in the original article; (2) provided more detail regarding the measures used; (3) added an analysis to confirm participants sleep during the Sleep condition night represented their typical sleeping patterns, and (4) added text to the discussion where required by, for instance, those additional statistical analyses.

Abstract

Standard replacement therapy for Addison's disease (AD) does not restore a normal circadian rhythm. Periods of sub- and supra- physiological cortisol levels experienced by patients with AD likely induce disrupted sleep. Given that healthy sleep plays an important role in memory consolidation, the novelty of the current study was to characterise, using objective measures, the relationship between sleep and memory in patients with AD, and to examine the hypothesis that poor sleep is a biological mechanism underlying memory impairment in those patients. We used a within-subjects design. Ten patients with AD and 10 matched healthy controls completed standardised neuropsychological tests assessing declarative memory (Rey Auditory Verbal Learning Test (RAVLT) and Logical Memory Test (LM)) and procedural memory (Finger Tapping Task) before and after a period of actigraphy-measured sleep, and before and after a period of waking. Relative to healthy controls, patients with AD experienced disrupted sleep characterised by poorer sleep efficiency and more time spent awake. Patients also showed impaired verbal learning and memory relative to healthy controls ($p = .007$). Furthermore, whereas healthy controls' declarative memory performance benefited from a period of sleep compared to waking (RAVLT: $p = .032$; LM: $p = .018$), patients with AD derived no such benefit from sleep (RAVLT: $p = .448$; LM: $p = .838$). Regarding the procedural memory task, analyses detected no significant between-group differences (all p 's $< .065$), and neither group showed significant sleep-enhanced performance. We demonstrated, using actigraphy and standardized measures of memory performance, an association between sleep disturbances and cognitive deficits in patients with AD. These results suggest that, in patients with AD, the source of memory deficits is, at least to some extent, disrupted sleep patterns that interfere with optimal consolidation of previously-learned declarative information. Hence, treating the sleep

disturbances that are frequently experienced by patients with AD may improve their cognitive functioning.

Keywords: Addison's disease, cortisol, sleep, memory

Introduction

We aimed to quantify and describe sleep quality and memory functioning in a sample of patients with AD and healthy controls, and to explore whether, in both groups, a period of sleep benefits memory consolidation as much as a period of waking does. AD is a rare endocrine disorder, characterized by decreased production of glucocorticoids and mineralocorticoids, typically resulting from destruction of the adrenal cortex. Even when using standard replacement-medication regimens (e.g., oral hydrocortisone and fludrocortisone), patients with AD experience cognitive impairments (e.g., poor memory) and behavioral irregularities (e.g., sleep disturbances) that impact negatively on their quality of life (Ten et al., 2001; Tytherleigh et al., 2004). Although there is a strong relationship between healthy sleep and optimal memory performance (Dudai et al., 2015), only one previous study explored the association between sleep quality and cognitive functioning in patients with AD (Henry, Wolf, Ross, & Thomas, 2015). In that study, data from self-report questionnaires and latent variable modeling suggested that poor quality of life, depressed mood, and memory impairment may be mediated by sleep disruption in AD. Although that study was limited in that it used only self-report measures, and in that it focused on general cognition rather than on theoretically-specified cognitive domains (e.g., memory), it nonetheless provided impetus for the current investigation. The novelty of the current study is that it uses objective measures of both sleep and memory to characterize the relationship between the two, and to examine the suggestion that poor sleep is a biological mechanism underlying memory impairment in patients with AD.

Under normal physiological circumstances, the orderly night-time sequencing of, and transitions between, SWS and REM sleep, provide optimal conditions for memory consolidation (Diekelmann & Born, 2010). This process of consolidation begins during SWS, when favorable

physiological conditions (e.g., slow oscillations in neocortical networks, HPA axis suppression) allow the replay and reactivation of memory traces encoded during waking (Born et al., 2006). Then, during REM sleep, similarly favorable physiological conditions (e.g., suppression of norepinephrine, increased levels of acetylcholine and serotonin, ponto-geniculo-occipital and theta waves, potentiation of expression of Immunoglobulin E) allow these reactivated memory traces to be integrated with pre-existing knowledge networks, thereby facilitating long-term potentiation (Walker & Stickgold, 2010). Cortisol plays a key role in initiating and maintaining these different sleep stages, accounting for its influence on the success of memory consolidation during healthy sleep (Bennion et al., 2015).

Patients with AD, even when on replacement therapy, report disrupted sleep and experience altered sleep architecture (Gillin et al., 1974a). For instance, Lovas and colleagues (2003) found that one-third of their sample of patients with AD reported weekly sleep disturbances, while just over 10% reported repeated awakenings and difficulty falling asleep. In a polysomnographic study, García-Borreguero and colleagues (2000) found that patients with AD who took a dose of hydrocortisone just before bedtime had fewer night-time awakenings and reduced REM latency, and spent more time in REM sleep, compared to patients whose medication had been withheld for 1.5 days.

These disrupted sleep patterns may arise because patients with AD, despite hydrocortisone replacement, do not exhibit normal diurnal cortisol variation. These patients have extremely low cortisol levels before their morning dose of hydrocortisone (with lower-than-normal levels between midnight and the early hours of the morning). After taking the medication, cortisol concentrations increase rapidly at first, but then decline quickly due to a short half-life of approximately 2 hours (Harbeck et al., 2009). This pattern contrasts with that of

healthy individuals, whose cortisol secretion is in a pulsatile, but circadian, rhythm (Young, Abelson, & Lightman, 2004).

The relationship between cognition and circulating glucocorticoids typically follows an inverted U-shaped pattern. Specifically, a certain level of cortisol is needed to enhance cognitive functioning; decreases below or increases beyond the threshold of optimal functioning impair cognition (McEwen, 1997). Numerous studies have shown that, in healthy adults, elevated cortisol levels are associated with impaired memory performance (Smeets, 2011). In neurobiologically similar fashion, variable sub- and supra-physiological concentrations of cortisol could also play an important role in the impaired cognitive functioning that is often characteristic of patients with AD. Recent literature suggests that patients with AD experience particular difficulties on verbal learning and memory tests (e.g., Henry et al., 2014; Schultebrasucks et al., 2015; Tiemensma et al., 2016). Due to this known association between altered cortisol and impaired performance on standardized memory tests, objective assessment of other factors (e.g., disrupted sleep) that might contribute to deficient memory performance in patients with AD is especially pertinent.

The Current Study

Patients with AD frequently experience sleep complaints and memory deficits. However, no published study has used objective measures to investigate disrupted sleep as a possible mechanism underlying the memory deficits observed in these patients. We thus aimed to quantify and describe sleep quality and memory functioning in a sample of patients with AD and healthy controls, and to explore whether sleep augments memory consolidation in patients as it does in controls. Based on literature suggesting that (a) cortisol plays a key role in maintaining the integrity of sleep architecture, (b) sleep plays an important role in cognitive functioning, and

(c) hydrocortisone replacement medication used by patients with AD does not restore the natural circadian rhythm and has direct effects on sleep architecture, we hypothesised that:

- (1) Patients with AD may report and experience disrupted, poor-quality sleep compared to healthy controls;
- (2) Healthy controls' memory performance may be enhanced by sleep, whereas patients' performance will derive no such benefit.

Methods and Materials

Study Design

This was a repeated-measures quasi-experimental study, featuring two groups of participants: Patients with AD and healthy controls. Each participant experienced two experimental protocols: a *Sleep* condition, where a period of sleep separated learning and recall of memory material, and a *Wake* condition, where a period of wakefulness separated learning and recall. Presentation of the conditions was counterbalanced across participants. Administration of the two protocols was separated by 1 week, during which participants wore an actigraph and kept sleep diaries.

The independent variables were group, with two levels of variation (patients with AD versus healthy controls), and memory consolidation condition, with two levels of variation (*Sleep* versus *Wake*). The two broad classes of dependent variables were (a) objectively-measured memory performance, and (b) objectively-measured sleep quality.

Participants

Participants were 10 adult patients with AD and 10 community-dwelling adults who were free of any chronic illness. We matched the groups on age, education (within 1-3 years), as well as sex and race distribution (each group included 2 men and 8 women, and 8 white and 2 mixed-

ancestry individuals). We recruited patients from the South African Addison's Disease database (SAAD; Ross et al., 2010). The diagnosis of AD was made on the basis of suggestive clinical presentation, low basal cortisol level and simultaneously elevated ACTH concentration, or, where indicated, a peak cortisol following 250 µg ACTH stimulation of less than 550 nmol/L associated with a basal raised plasma ACTH exceeding 10.1 pmol/L (Ross et al., 2010). We recruited healthy controls using posters (see Appendix F) placed on noticeboards around the university community and in the nearby offices of large corporations.

Exclusion criteria applied to all participants were (1) age (we excluded individuals younger than 18 and older than 55 years because there are age-related effects on sleep architecture; Skeldon et al., 2016); (2) the presence of severe depressive symptomatology (HPA-axis hypersecretion and disrupted sleep are frequently-encountered symptoms of depression; Palagini, Baglioni, Ciapparelli, Gemignani, & Riemann, 2013; Steiger, 2002); (3) measured IQ at 1 standard deviation below average (lower IQ might have negative effects on memory test performance); and (4) the presence of mild cognitive impairment or dementia. Exclusion criteria applied to all potential female participants were (1) menopause (menopausal women often experience disrupted sleep due to changes in their hormone levels; Antonijevic et al., 2000); (2) pregnancy (there are alterations in REM sleep and sleep quality depending on the trimester of pregnancy; Brunner, Münch, Biedermann, & Huch, 1994; Ko, Chang, & Chen, 2010); and (3) oral contraceptive use (women who take oral contraceptives have significantly raised cortisol-binding globulin; Kirschbaum et al., 1999).

Healthy controls were free of any chronic medical or psychiatric illnesses, but this was not the case for patients with AD. We made this decision given that psychiatric and medical

conditions are relatively common within this population (Anglin et al., 2006), and our sample size was already limited.

Figure 9 presents the flow of patients through the recruitment process.

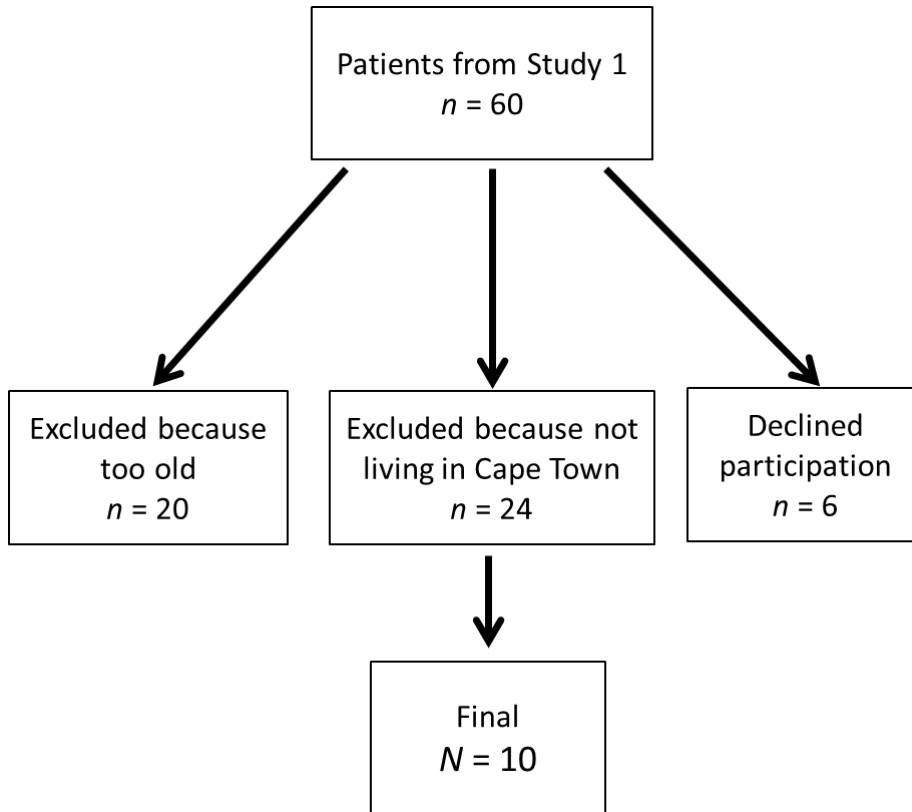


Figure 9. Flow of patients with AD through the recruitment and study processes.

We confirmed our AD sample was representative of the entire SAAD cohort: a one-sample t -test detected no significant differences for total hydrocortisone dose, $t(9) = -0.79$, $p = .450$, and χ^2 goodness-of-fit tests detected no significant differences in terms of race distribution, $\chi^2(3) = 1.17$, $p = .761$, or sex distribution, $\chi^2(1) = 1.38$, $p = .241$. There was, however, a significant difference for age, $t(9) = -2.42$, $p = .039$, which arose because of our stringent exclusion criteria. Patients in the current study were younger than those in the SAAD cohort ($M = 42 \pm 10.07$ versus 51.9 ± 20.84 years).

Measures

Sociodemographic and medical questionnaire (see Appendices C and D). This measure elicited data about (a) demographic characteristics (e.g., age, race, household income), (b) medical history, and (c) for patients with AD, type and dosage of current medication, and length of time since diagnosis. The demographic and clinical data were extracted from SAAD. We used a self-constructed medical questionnaire to corroborate the findings in the database.

Screening questionnaires.

Mini International Neuropsychiatric Interview (English version 5.0.0; MINI; Sheehan et al., 1998). The MINI is a well-established brief structured diagnostic interview tool that probes for the presence of major DSM-IV Axis I psychiatric disorders. It has good inter-rater and test-retest reliability, good validity in relation to other clinical interviews, and has been used extensively in psychological research in South Africa (Kaminer, Stein, Mbanga, & Zungu-Dirwayi, 2001). The MINI can be administered by a lay interviewer within approximately 15 minutes. Potential healthy control participants with any current psychiatric disorder were excluded from participation.

Beck Depression Inventory-Second Edition (BDI-II; Beck et al., 1996). The BDI-II is a 21-item instrument that measures intensity and severity of depression in respondents. Individuals with BDI-II scores greater than 29 (indicating severe depression) were excluded from participation.

Shipley-2 Intelligence Test (Shipley, Gruber, Martin, & Klein, 2009). This is a brief measure (20 minutes to complete) of general intellectual functioning that assesses both crystallized and fluid intelligence. Crystallised intelligence is the knowledge gained as a result of education and experience, whereas fluid intelligence is the ability to use logic to learn and

acquire new information. The *Vocabulary* scale of the Shipley assesses crystallised intelligence, whereas the *Block Patterns* scale assesses fluid intelligence. For the *Vocabulary* test participants are given a list of 40 words in capital letters. Next to each capitalised word are four other words and participants are required to circle the word they believe has the same meaning as the word written in capital letters. This test has a time limit of 10 minutes. For the *Block Patterns* test participants are shown a series of 12 block patterns. Each block pattern has the same pattern alongside it, with a missing piece/pieces. Participants are required to choose from a series of smaller pieces which one will complete the pattern. This test also has a time limit of 10 minutes.

The Shipley-2 has proven a reliable and valid estimate of overall intellectual functioning. Psychometric studies indicate that the *Vocabulary* scale has a high degree of internal consistency (alpha values ranging from 0.85 to 0.92), as does the *Block Patterns* scale (alpha values ranging from 0.88 to 0.94). In addition, the Shipley-2 has high test-retest reliability (Shipley et al., 2009).

Individuals with a Shipley IQ score below 85 (i.e., below the norm-defined average range) were excluded from participation.

Objective cognitive tests.

Rey Auditory-Verbal Learning Test (RAVLT; Lezak et al., 2004). The RAVLT measures verbal learning and memory. Participants were read the same 15-item word list five times, and after each presentation were asked to recall as many words as possible. After presentation and recall of an interference list, participants were again asked to recall as many words as possible from the original list. Twelve hours later, they were once again asked to recall as many words as possible from the original list.

Logical Memory (LM; Wechsler, 1997b). The LM subtest of the Wechsler Memory Scale (WMS) measures verbal memory and was used to supplement episodic memory testing.

The examiner read two stories, each containing numerous distinct thematic elements, to the participant. After each story, the examiner stopped and asked the participant to give an account of all the elements that s/he could remember from the story. Administration of the second story was repeated immediately after its initial presentation. Delayed recall of both stories was tested 12 hours later (Lezak et al., 2004).

Finger Tapping Task (FTT; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002).

The FTT is a computerized assessment of procedural memory. Participants were required to type a 5-digit sequence repeatedly, using their non-dominant hand and as accurately and as quickly as possible, for 30 seconds. The sequence appeared on screen at all times to avoid reliance on working memory. The training session consisted of 12 such trials, with a 30-s fixation period separating each trial. Twelve hours later, participants performed a 3-trial re-test session.

We used parallel RAVLT, LM (see Sullivan, 2005), and FTT forms in the *Sleep* and *Wake* conditions.

Actigraph. We used the GT3X+ (512MB) Activity Monitor. Participants wore the device on an elastic belt on the right hip continuously for 1 week. The actigraph records data such as the number of steps taken, light exposure, and body temperature. It is a valid and reliable measure of physical activity, with a reliability co-efficient of 0.99 (Tryon, 2005). Reliability increases the longer the device is worn, and the actigraph has proven a reliable alternative to laboratory-based PSG measures (Kushida et al., 2001). Here, we used the actigraph to record participants' movement and sleep patterns in a naturalistic environment over the 12-hour *Sleep* and 12-hour *Wake* condition periods.

Sleep diary. Although PSGs and actigraphs are reliable objective measures of sleep, the literature in this field suggests the additional use of subjective questionnaires to fully represent participants' sleeping habits (Kushida et al., 2001). Data from sleep diaries are strongly correlated with those from PSGs and actigraphs (Asaka & Takada, 2011). Here, we used the Pittsburgh Sleep Diary (Monk et al., 1994) to collect self-reported data regarding when participants in the *Sleep* condition went to sleep and awoke the next morning.

Procedure

Research ethics committees from the University of Cape Town's Department of Psychology and Faculty of Health Sciences, both of which adhere to the Declaration of Helsinki (World Medical Association, 2013), approved the study procedures.

All testing took place at participants' homes. Conditions were counterbalanced so that half the participants experienced the *Sleep* condition first and the *Wake* condition 1 week thereafter. In the *Wake* condition, participants were instructed not to sleep between the morning and evening memory testing sessions.

The study protocol began when the researcher arrived at the participant's home at either 7pm (*Sleep* condition; see Figure 10) or 7am (*Wake* condition; see Figure 11). After written informed consent (see Appendix G) was taken participants underwent the screening measures. They were then given the sleep diary and actigraph, with explanations about how to use each.

Participants then completed the RAVLT and LM learning and immediate recall trials and the FTT training trials. They completed the delayed recall and re-test trials 12 hours later (i.e., at 7am the next day if they were in the *Sleep* condition, or at 7pm the same day if they were in the *Wake* condition). Patients were instructed to take their morning dose of medication 1 hour before testing, to ensure results were not confounded by insufficient cortisol concentrations. They were

also instructed to take their afternoon/evening dose at their usual time, to ensure we provided a real reflection of their daily lives. The average time between last HC intake and the evening testing session was 4.57 hours ($SD = 3.41$). It should be noted that three patients took their last HC dose after the evening testing had occurred (as this was their normal medication regime). We obtained verbal confirmation that patients took their medication.

One week later, the researcher again visited the participant's home and repeated the procedure outlined above, in counterbalanced order.

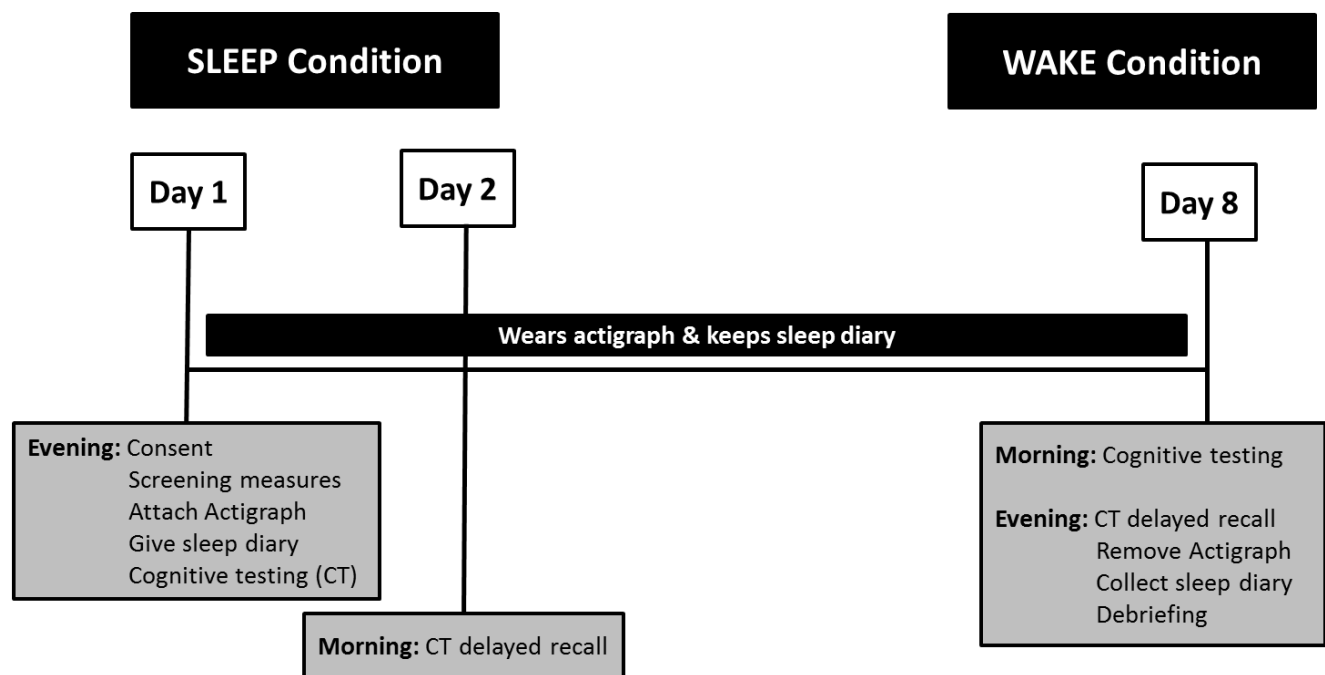


Figure 10. Study procedure (counterbalanced with Sleep Condition first).

- (2) Percent Retention: number of story elements recalled correctly the delayed recall trial divided by number of story elements recalled during Learning, expressed as a percentage.

We scored the FTT following procedures described by Walker et al. (2002), and derived these outcome variables:

- (1) Post-training Performance: average number of completed sequences across the last three trials of the training session.
- (2) Post-training Error Rate: average number of errors across the last three trials of the training session.
- (3) Percent Retention: average number of completed sequences across the three re-test trials divided by Post-Training Performance, expressed as a percentage.
- (4) Change in Error Rate: average number of errors across the three re-test trials minus Post-Training Error Rate.

To characterize participants' sleep patterns on the night of the *Sleep* condition, we used data from the sleep diaries (to determine when participants turned out the lights at night, and when they awoke in the morning) and from the actigraph (provided by the device's automated scoring software). We derived five outcome variables from the actigraph data collected in the period between diarized sleep onset and waking:

- (1) Sleep Latency: number of minutes between when the participant turned out his/her lights at night and when s/he fell asleep (sleep onset).

- (2) Total Sleep Time (TST): number of minutes the participant spent sleeping in the period between sleep onset and when s/he awoke in the morning (waking).
- (3) Wake After Sleep Onset (WASO): number of minutes the participant spent awake in the period between sleep onset and waking.
- (4) Sleep Efficiency: TST divided by (TST + WASO).
- (5) Number of Awakenings: the number of times the participant awoke for more than 1 minute in the period between sleep onset and waking.

Power analysis and sample selection. A power analysis suggested that the sample size be set at $N = 18$ ($n = 9$ per group) if we wanted to achieve statistical power $> .90$ using a repeated-measures ANOVA investigating between- and within -group differences (parameters: correlation among repeated measures = .5; effect size = medium, Cohen's $f = .25$; $\alpha = .05$; Erdfelder et al., 1996).

Inferential statistical analyses. We completed all analyses using R (the `Exact` package) and SPSS (version 22). Unless noted otherwise, we set the threshold for statistical significance (α) at .05. For each of the analyses described below, we calculated the appropriate effect size estimate, and we interpreted these estimates following convention (e.g., for Cohen's d , 0.20-0.30 = small; 0.50 = medium; > 0.80 = large; Cohen, 1992) . Where assumptions underlying inferential statistical tests were violated, we used the appropriate non-parametric tests.

The analyses proceeded across six stages. First, a series of dependent sample t -tests⁸ compared group demographic characteristics. Second, a series of dependent sample t -tests tested

⁸ The results of the same analyses using independent sample t -tests are presented in Appendix H.

the predictions that, for sleep variables, (a) Sleep Latency, WASO, and Number of Awakenings, Healthy Controls < AD, and (b) TST and Sleep Efficiency, Healthy Controls > AD. A Bonferroni correction controlled for inflated familywise error associated with multiple pairwise comparisons; in this case, $\alpha = .05 / 5 = .01$. Third, a series of 2 x 2 (Group [AD versus Healthy Controls] x Condition [Sleep versus Wake]) repeated-measures ANOVAs assessed between- and within-group differences on the RAVLT, LM and FTT outcome variables. A Bonferroni correction again controlled for multiple pairwise comparisons; in this case, $\alpha = .05 / 8 = .006$. Fourth, a series of Pearson's correlation analyses assessed whether (a) within each group, demographic (age and BMI) variables were associated with sleep variables, (b) within each group, demographic (age, education, and IQ) variables were associated with cognitive variables, and (c) in the AD group only, disease characteristics (i.e., time since diagnosis, total hydrocortisone dose, dose/kg, and number of doses/day) were associated with sleep/cognitive variables. Fifth, a series of Fisher's exact tests assessed, within the AD group only, whether timing of last hydrocortisone dose was associated with sleep/cognitive variables. Lastly, we ran an additional set of secondary analyses to determine whether the presence of comorbid illnesses in patients with AD influenced their cognitive functioning or sleep. A series of independent sample *t*-tests compared cognitive and sleep variables in patients with and without several comorbid illnesses.

Results

Sample Characteristics

Table 8 presents the demographic characteristics of our sample, as well as their BDI-II and Shipley IQ data.

Table 8
Sample Demographic Characteristics (N = 20)

Characteristic	Group		Test statistic	<i>p</i>	ESE
	AD (<i>n</i> = 10)	Healthy (<i>n</i> = 10)			
Age (years)	42.00 (10.07)	40.30 (11.62)	<i>t</i> (9) = 1.45	.182	0.16
Education (years)	13.80 (2.44)	13.50 (1.58)	<i>t</i> (9) = 0.30	.769	0.15
BMI	28.94 (5.29) ^a	23.40 (2.31)	<i>t</i> (5) = 4.13	.009*	1.51
Income (ZAR/month)			$\chi^2(4) = 4.40$.384	.355
2500 – 5499	10 (1)	0 (0)			
5500 – 9999	10 (1)	0 (0)			
10000 – 19999	30 (3)	10 (1)			
20000 – 30000	10 (1)	30 (3)			
30000+	40 (4)	60 (6)			
BDI-II					
Time 1	9.90 (7.91)	7.70 (5.76)	<i>t</i> (9) = 0.61	.559	0.32
Time 2	7.89 (7.61) ^b	7.22 (8.14) ^c	<i>t</i> (8) = 0.16	.878	0.09
Shipley IQ	94.50 (15.31)	105.70 (11.35)	<i>t</i> (9) = -2.40	.040*	0.83

Note. For all variables except Income, means are provided with standard deviations in parentheses. For Income, data provided are % of sample with *n* in parentheses. BMI = body mass index. BDI-II = Beck Depression Inventory – Second Edition. ESE = effect size estimate; in this case, Cohen's *d* for *t*-tests and Cramer's *V* for chi-square.

^aData based on 6 participants (4 patients did not provide information on their height).

^bData based on 9 participants (1 patient did not complete this measure at Time 2).

^cData based on 9 participants (1 participant did not complete this measure at Time 2).

**p* < .05.

By design, there were no significant between-group differences in terms of age (*p* = .182), income (*p* = .384), education (*p* = .769), sex distribution, and race distribution. It did, however, detect significant between-group differences in terms of BMI (*p* = .009) and IQ (*p* = .040). On average, patients had significantly higher BMI scores than healthy controls (*M* = 94.5, range = 86-118 vs *M* = 105.7, range 116-130, respectively), and significantly lower IQ scores than healthy controls (*M* = 28.94, range = 23.14 - 37.55 vs *M* = 23.40, range 19.26 - 26.37, respectively).

Regarding BDI-II scores, analyses detected no significant between-group differences, at either the first (*p* = .559) or second (*p* = .878) measurement point. Of note here is that (a) across

the sample, scores were relatively stable from one measurement point to the next (test-retest reliability = .87), and (b) within each group, the average BDI-II score fell in the range conventionally described as “minimally depressed” (0-13 points; Beck et al., 1996).

Table 9 presents details regarding the clinical characteristics and medication regimen of patients with AD. All were taking short-acting hydrocortisone. 3 patients had hypothyroidism, and each of the following comorbidities was present in 1 patient: fibromyalgia, high cholesterol, hypertension, diabetes, asthma, irritable bowel syndrome, psoriasis.

Table 9

Clinical and Medication Characteristics of Patients with Addison’s Disease (N = 10)

Characteristic	<i>M (SD)</i>	Range
Clinical		
Age at diagnosis (yrs)	26.33 (13.64) ^a	7 – 54 ^a
Time since diagnosis (yrs)	16.00 (9.95) ^a	1 - 34 ^a
Number of other illnesses [*]	1.30 (2.21)	0 – 7
None, % of sample (<i>n</i>)	50 (5)	
One, % of sample (<i>n</i>)	30 (3)	
> One, % of sample (<i>n</i>)	20 (2)	
Medication		
Total hydrocortisone (HC) dose (mg)	21.50 (6.69)	15 – 35
Hydrocortisone/kg	0.26 (0.10) ^b	0.17 - 0.46
Number of HC doses per day	2.00 (0.47)	1 – 3
One, % of sample (<i>n</i>)	10 (1)	
Two, % of sample (<i>n</i>)	80 (8)	
Three, % of sample (<i>n</i>)	10 (1)	
Time of last HC dose, % of sample (<i>n</i>)		
Morning	10 (1)	
1pm – 4:59pm	50 (5)	
5pm – 7pm	10 (1)	
After 7pm	30 (3)	

Note. ^aData based on 10 participants (1 patient did not provide information on their age at diagnosis). ^bData based on 10 participants (1 patient did not provide information on their weight).

Between-group Comparisons: Sleep Data

To confirm that participants sleep during the *Sleep* condition night was representative of their typical sleeping patterns we conducted within-group comparisons of sleep outcome variables on the *Sleep* condition night to the average of those on the other 6 nights of data collection. Within both the AD and healthy control groups, analyses detected no significant differences, for any of the sleep outcome variables, between the *Sleep* condition night and the average of the other 6 nights (AD group: all $ps > .214$; Healthy Control group: all $ps > .101$). These data confirm that during the 12-hour *Sleep* condition, participants sleeping patterns were representative of their typical night's sleep.

Table 10 presents descriptive data for participants' activity during the *Sleep* condition, as well as the results of statistical analyses testing the prediction that, for all sleep variables, healthy controls would experience more favourable outcomes.

Table 10
Participants' Activity During the Sleep Condition (N = 16)

Outcome variable	AD ($n = 8$) ^a	Healthy ($n = 8$) ^b	Test statistic	p	ESE
Total Sleep Time (mins.)	440.00 (72.42)	396.25 (52.09)	$t = 1.96$.046	0.69
Sleep Latency (mins.)	9.38 (15.37)	1.88 (3.72)	$t = 1.61$.076	0.67
WASO (mins.) ^c	28.38 (28.11)	7.63 (12.74)	$z = -2.37$.009*	0.59
Sleep Efficiency (%)	91.78 (4.26)	97.18 (2.69)	$t = -3.12$.009*	1.52
Number of Awakenings ^c	3.00 (2.61)	0.75 (0.89)	$z = -1.89$.029	0.47

Note. Means are presented, with standard deviations in parentheses. All p -values presented are one-tailed.

AD = Addison's disease; WASO = wake after sleep onset; ESE = effect size estimate; in this case, Cohen's d for the dependent samples t -tests and z/\sqrt{N} for Wilcoxon Signed Ranks tests.

^aOf the initial sample of 10 patients with AD, two did not complete the diary and did not wear the actigraph on the Sleep Condition night.

^bOf the initial sample of 10 healthy controls, two did not wear the actigraph on the Sleep Condition night.

^cWilcoxon Signed Ranks test performed.

* $p < .01$ (statistically significant after the Bonferroni correction).

As the table shows, the analyses detected significant-between-group differences with regard to WASO ($p = .009$) and Sleep Efficiency ($p = .009$). The descriptive statistics suggest that, on average, healthy controls achieved a full night of relatively uninterrupted sleep, whereas patients experienced interrupted sleep characterised by poorer sleep efficiency and more time spent awake.

Between- and Within-group Comparisons: Cognitive Tests

Table 11 presents descriptive data regarding RAVLT, LM and FTT performance, divided by group and condition.

Table 11
Memory Performance: AD and Healthy Control Participants in Sleep and Wake Conditions (N = 20)

Variable	AD ($n = 10$)		Healthy Control ($n = 10$)	
	Sleep	Wake	Sleep	Wake
Auditory-Verbal Learning Test				
Learning	52.60 (11.38)	54.10 (9.37)	60.10 (6.59)	58.70 (7.62)
Percent Retention	61.98 (22.58)	53.64 (25.39)	83.21 (12.30)	72.88 (11.01)
Logical Memory Test				
Learning	29.60 (10.36)	30.80 (9.07)	33.90 (6.59)	33.40 (5.25)
Percent Retention	55.82 (18.52)	57.43 (17.01)	71.12 (13.22)	54.14 (20.04)
Finger Tapping Task				
Post-training Performance	18.53 (6.14)	17.97 (6.31)	19.07 (2.24)	17.60 (2.96)
Post-training Error Rate	0.05 (0.04)	0.04 (0.05)	0.02 (0.02)	0.03 (0.02)
Percent Retention	105.58 (13.64) ^a	101.30 (12.98)	107.02 (13.99)	108.58 (12.56)
Change in Error Rate	-0.011 (0.02) ^a	0.004 (0.08) ^a	-0.002 (0.03)	-0.004 (0.02)

Note. Means are presented, with standard deviations in parentheses.

^aData based on 9 participants (1 patient pressed the incorrect keys throughout the session).

Declarative memory: RAVLT performance. Regarding the Learning variable, the analysis detected no significant main effect of Condition, $F(1, 18) = 0.01$, $p = .971$, $\eta_p^2 < .01$, or of Group, $F(1, 18) = 2.59$, $p = .125$, $\eta_p^2 = .13$, and no significant Group x Condition interaction, $F(1, 18) = 1.15$, $p = .298$, $\eta_p^2 = .06$. The descriptive statistics shown in Table 11, suggest that, regardless of condition, healthy controls learnt more words than did patients. Regarding the

Percent Retention variable, the analysis detected a significant main effect of Group, $F(1,18) = 9.39, p = .007, \eta_p^2 = .34$, but no significant main effect of Condition, $F(1, 18) = 3.14, p = .093, \eta_p^2 = .15$, and no significant Group x Condition interaction, $F(1,18) = 0.04, p = .852, \eta_p^2 < .01$.

Regarding that main effect, the descriptive statistics shown in Table 11 suggest that, regardless of condition, healthy controls retained significantly more words than did patients. Of note is that this main effect did not remain significant after the Bonferroni correction. The descriptive statistics also suggest that participants, regardless of group assignment, retained more information when in the *Sleep* than in the *Wake* condition.

Given that our main aim was to explore the impact of sleep (versus waking) on memory performance, we explored the main effect of Condition further by conducting within-group post-hoc pairwise comparisons. Those analyses detected a significant between-condition difference within the Healthy Control group ($p = .032$), but no significant between-condition difference within the AD group ($p = .448$). Together, these data suggest that (a) healthy controls retained significantly more information when a period of sleep, rather than waking, separated learning from recall, but (b) patients derived no such benefit (see Figure 12).

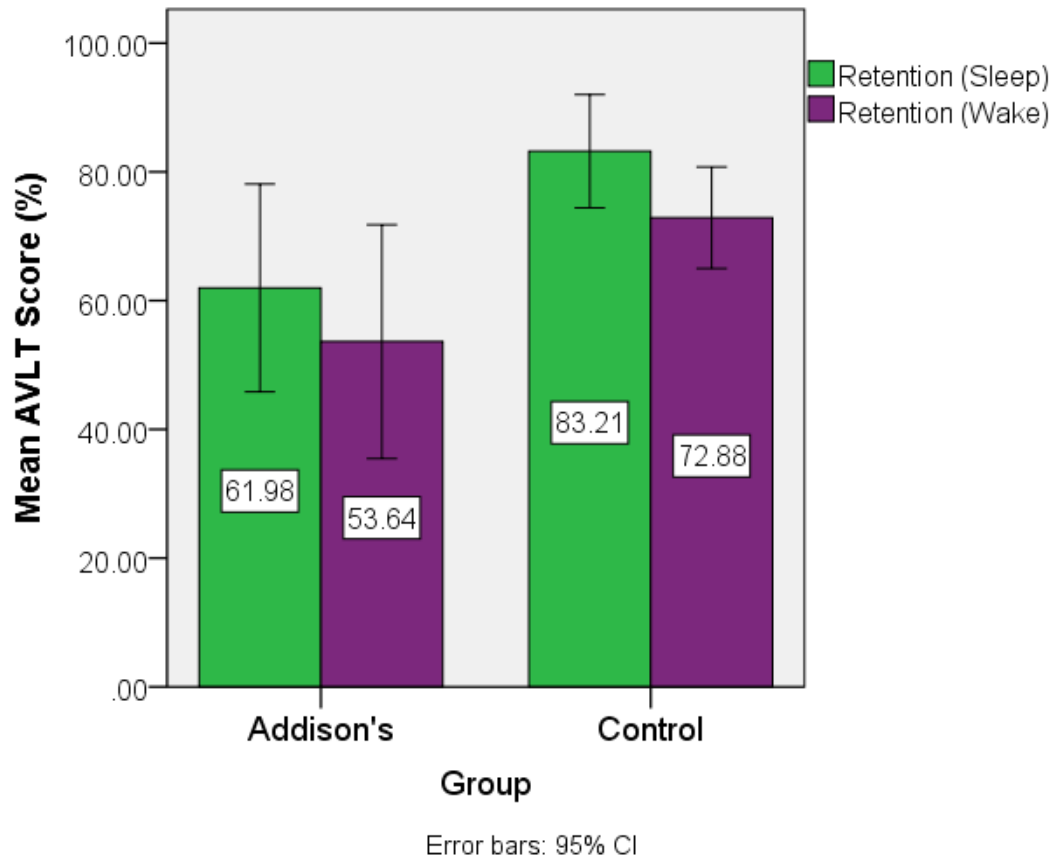


Figure 12. RAVLT performance between patients with AD and controls during a period of sleep versus a period of wake.

Declarative memory: LM performance. Regarding the Learning variable, the analysis detected no significant main effect of Condition, $F(1,18) = 0.15, p = .705, \eta_p^2 = .01$, or of Group, $F(1,18) = 0.98, p = .336, \eta_p^2 = .05$, and no significant Group x Condition interaction, $F(1,18) = 0.87, p = .363, \eta_p^2 = .05$. Descriptive statistics shown in Table 11 suggest that, regardless of condition, healthy controls retained significantly more words than did patients. The descriptive statistics also suggest that Control participants retained more information when in the *Sleep* than in the *Wake* condition, however patients actually retained more information when in the *Wake* than in the *Sleep* condition.

Regarding the Percent Retention outcome variable, the analysis detected a significant Group x Condition interaction, $F(1,18) = 4.71, p = .044, \eta_p^2 = .21$, but no significant main effect of Condition, $F(1,18) = 3.22, p = .089, \eta_p^2 = .15$, or Group, $F(1,18) = 0.86, p = .367, \eta_p^2 = .05$. To explore this significant interaction effect further, we conducted within-group post-hoc pairwise comparisons. These analyses detected a significant between-condition difference within the healthy control group, $p = .018$, but no significant between-condition difference within the AD group, $p = .838$. Together, these data suggest that healthy control participants retained significantly more information when a period of sleep, rather than waking, separated learning from recall. In contrast, patients with AD derived no such benefit (see Figure 13).

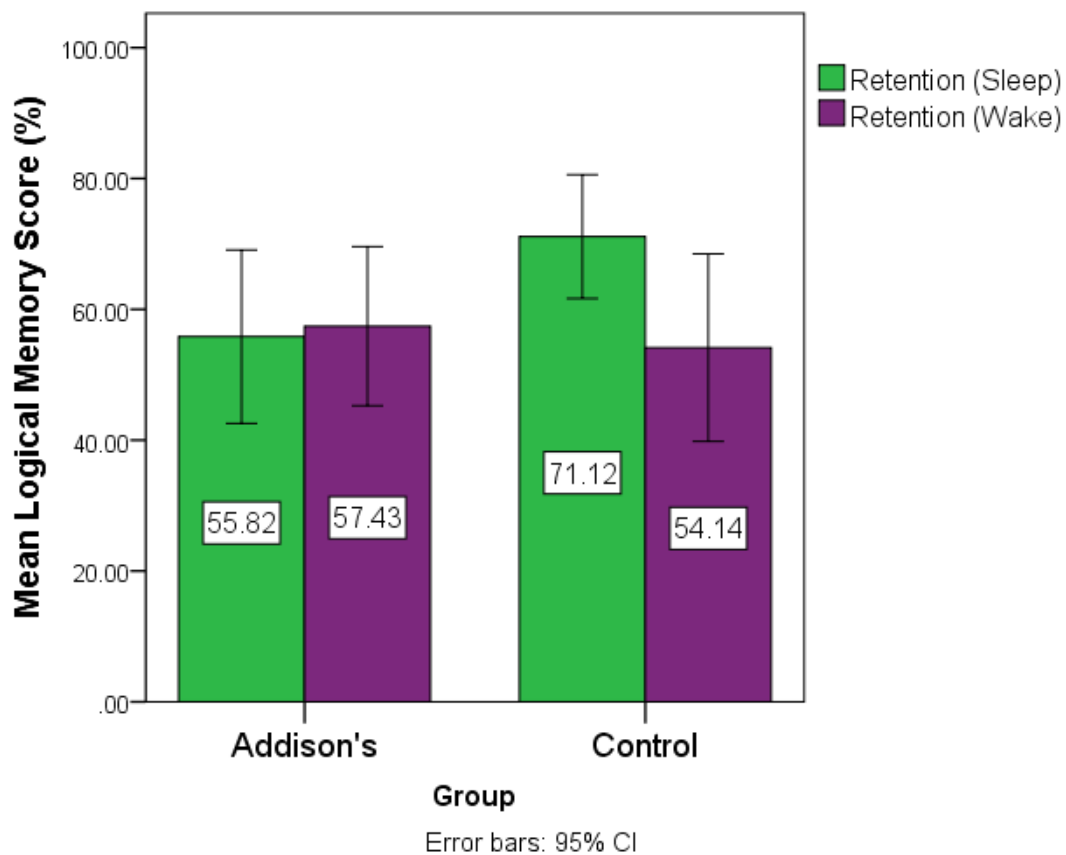


Figure 13. Logical memory performance between patients with AD and controls during a period of sleep versus a period of wake.

Procedural memory: FTT performance. The analyses detected no significant main effects of Group, no significant main effects of Condition, and no significant Group x Condition interactions, for any of the FTT variables, $F_s < 3.83$, $p_s > .065$, $\eta_p^2s < .19$.

Associations between Demographic/Clinical Characteristics and Sleep/Cognitive Variables

Within each group, we calculated associations between demographic (age, education, IQ) variables and each of the eight cognitive performance variables, and between demographic (age and BMI) variables and each of the five sleep variables.

Associations between demographic and cognitive variables. Within the AD group, the analyses detected positive associations between (i) education and (a) LM Learning in the *Sleep* condition ($r = .86$, $p < .001$) and in *Wake* condition ($r = .85$, $p = .002$), (b) LM Percent Retention in the *Sleep* condition ($r = .65$, $p = .044$) and in the *Wake* condition ($r = .71$, $p = .020$), (c) FTT Post-training Performance in the *Sleep* condition ($r = .70$, $p = .024$) and in the *Wake* condition ($r = .71$, $p = .022$); and (ii) IQ and LM Percent Retention in the *Sleep* condition ($r = .63$, $p = .050$) in the *Wake* condition ($r = .82$, $p = .004$), and (b) FTT Post-training Performance in the *Sleep* condition ($r = .85$, $p = .001$) and in the *Wake* condition ($r = .77$, $p = .004$).

Within the Healthy Control group, the analyses detected positive associations between (i) age and (a) FTT Post-training Performance in the *Sleep* condition ($r = .78$, $p = .008$) and in the *Wake* condition ($r = .82$, $p = .004$).

Associations between demographic and sleep variables. Within the AD group, the analyses detected no significant associations. Within the Healthy Control group, the analyses detected negative associations between Sleep Latency and (a) age ($r = -.69$, $p = .029$), and (b) BMI ($r = -.85$, $p = .004$).

Associations between Disease Characteristics and Cognitive Variables

Within the AD group, we calculated associations between disease characteristics and each of the eight cognitive variables. The analyses detected (i) negative associations between disease duration and (a) RAVLT Learning, in both the *Sleep* and *Wake* conditions ($r = -.63, p = .034$, and $r = -.75, p = .010$ respectively), and (b) LM learning in both the *Sleep* and *Wake* conditions ($r = -.70, p = .019$, and $r = -.67, p = .024$ respectively).

Associations between Disease Characteristics and Sleep Variables

Within the AD group, we calculated associations between disease characteristics and each of the five sleep variables. The analyses detected (i) positive associations between (a) age at diagnosis and sleep efficiency ($r = .64, p = .044$), and (b) number of doses and WASO ($r = .77, p = .013$); (ii) a negative association between total hydrocortisone dose and Sleep Efficiency ($r = -.67, p = .034$); and (iii) associations between dose/kg and both Sleep Efficiency and Sleep Latency ($r = -.69, p = .042$, and $r = .82, p = .012$ respectively).

Finally, within the AD group, analyses detected no significant associations between timing of the last hydrocortisone dose (before 18h00, $n = 7$; after 18h00, $n = 3$) and (a) any of the sleep outcome variables, and (b) any of the cognitive performance variables, $ps > .120$, $Vs < 1.00$.

Secondary Analyses

We ran an additional set of secondary analyses to determine whether the presence of comorbid illnesses in patients with AD influenced their cognitive functioning or sleep.

Regarding psychiatric conditions in the AD group, MINI structured interviews suggested that two patients could be diagnosed with generalised anxiety disorder, two with agoraphobia, and one with current manic episodes. By and large, however, these psychiatric comorbidities

appeared to have little influence on sleep and cognitive outcome variables: Analyses detected only one significant difference (RAVLT Percent Retention scores in the Sleep condition) between patients with and without psychiatric comorbidity, $t(9) = -2.88, p = .022$. Here, the mean score of patients with psychiatric comorbidities was significantly higher. The most common comorbid medical condition in patients with AD was hypothyroidism (30%, 3 people; followed by fibromyalgia, high cholesterol, hypertension, diabetes, asthma, irritable bowel syndrome, and psoriasis (10%, 1 person had each of these illnesses). Analyses detected only one significant difference (sleep efficiency) between patients with and without medical comorbidities, $t(9) = -3.33, p = .016$. Here, the mean score of patients with medical comorbidities was significantly higher. Hence, in this limited sample, it does not appear that the presence of comorbid illnesses has a substantial impact on cognitive functioning or sleep in patients with AD.

Discussion

Previously published studies report that patients with AD, even when on replacement therapy, frequently present with sleep complaints and memory deficits (Henry et al., 2015; Løvås et al., 2003; Tiemensma et al., 2016). However, this study is the first to use objective measures in an investigation of whether disrupted sleep might serve as a mechanism underlying the memory deficits observed in patients with AD. Our analyses confirmed that these patients experience disrupted, poor-quality sleep compared to healthy controls, and that whereas controls' memory performance benefitted from a period of sleep relative to waking, patients derived no such benefit. In concert with previous literature indicating that (a) cortisol plays a key role in maintaining the integrity of sleep patterns, and (b) healthy sleep plays an important role in memory consolidation, our results suggest that, in patients using hydrocortisone medication,

memory deficits might be associated, at least partially, with disrupted sleep patterns that interfere with optimal consolidation of previously-learned information.

Our actigraph data for patients with AD present a pattern consistent with, for instance, Løvås et al. (2003) and Henry et al. (2015), who found that their samples of patients with AD reported frequent sleep disturbances, including difficulty falling asleep, repeated awakenings, and reduced sleep quality. In both of those studies, as in the current study, all patients were on replacement therapy. Nonetheless, their patterns of cortisol secretion would still not match those of healthy individuals (Ross et al., 2013). In light of the fact that cortisol plays an important role in regulating circadian rhythms and in ensuring smooth transitions between sleep stages (Steiger, 2002), it is unsurprising that patients with AD, even when on replacement therapy, experience poor-quality sleep.

Individuals who experience poor-quality sleep frequently display compromised cognitive functioning (and, in particular, less-than-optimal memory consolidation), and numerous psychiatric conditions are marked by interrelated sleep and memory impairments (see, e.g., Lipinska, Timol, Kaminer, & Thomas, 2014). Given our confirmation of disrupted sleep patterns in the current sample of patients with AD, exploration of possible memory deficits in these patients was warranted.

Declarative memory performance was better in healthy controls than in patients. These results are consistent with a growing literature describing memory impairments in patients with AD (Henry et al., 2014; Schultebrasucks et al., 2015; Tiemensma et al., 2016). These impairments likely emerge not only from the indirect effects of disrupted cortisol secretion patterns (and consequent circadian rhythm and sleep disturbances), but also from the direct effects of periods of supra-physiological cortisol levels experienced by patients taking short-acting hydrocortisone

(Andela et al., 2015). Periods of supra-physiological glucocorticoid increases have particularly dramatic effects on brain regions with dense concentrations of glucocorticoid receptors, such as the hippocampus and the PFC (Kim & Diamond, 2002; Shansky & Lipps, 2013). These effects can include degeneration of hippocampal neurons (Sapolsky et al., 1986), altered dendritic organization in the PFC (Arnsten & Pliszka, 2011), and, consequently, impaired performance on declarative memory tasks (Arnsten, 2009; Payne et al., 1996).

We investigated the relationship between adrenal function, sleep, and cognitive performance because sleep and other circadian oscillators exert control over HPA-axis secretory activity and because the sequence of, and transitions between, sleep stages throughout the night is the foundation of successful consolidation of previously-learned information (Giuditta, 2014). Healthy controls' declarative memory retention benefited from a period of sleep compared to waking, whereas patients with AD derived no such benefit. This is a novel finding in the literature on cognitive functioning in patients with AD, and is consistent with a large body of literature indicating that a full night of uninterrupted sleep (i.e., of the kind experienced by healthy controls, but not patients, in this study), even when compared against an equal number of hours spent awake, has a positive effect on memory consolidation (see, e.g., Diekelmann & Born, 2010). Because patients with AD do not experience a normal circadian rhythm of cortisol, the sequence of, and transitions between, sleep stages throughout the night may not have occurred in the manner that is required for successful memory consolidation. An alternative explanation, however, is that patients with AD are generally fatigued, and that therefore poor performance spans across periods of sleep and waking. The design of the current study does not allow us to examine this latter prediction, however.

In contrast to the patterns of data on declarative memory tests and their relationships to patterns of sleep, we found no significant between-group or between-condition differences in procedural memory performance. One way to account for the discrepancy between findings regarding declarative and procedural memory tasks is that the former are hippocampal-dependent, whereas the latter are not. Given that hydrocortisone exposure affects hippocampal integrity, but does not affect areas typically associated with response-based sequence learning (e.g., motor cortex, caudate nucleus), it is plausible that procedural memory performance of patients with AD would be unimpaired. Regardless, no previous study has investigated procedural memory in patients with AD, and hence this suggestion that procedural memory is not impaired in patients with AD is a novel finding.

We also found that, in both groups, there were relatively equal gains in procedural memory performance after a period of sleep and a period of waking. This result is consistent with some previously published work (e.g., Fischer et al., 2002), but is not consistent with a larger number of studies reporting that the gain in performance following a period of wakefulness is not as robust as the gain following a period of sleep (e.g., Walker et al., 2002). One possible explanation for the discrepancy between our results and those reported in the latter papers is the age of our participants. All of those studies featured young adult participants (18-28 years), whereas our participants ranged in age from 20-55 years (median = 43.5). Given that there are age-related changes in the relationship between sleep and memory consolidation (Backhaus et al., 2007), it is possible that differences in procedural memory performance across periods of *Sleep* versus *Wake* are not as robust in middle-aged adults (Diekelmann et al., 2009).

Our series of secondary analyses suggested that, among healthy control participants, shorter sleep latency bore a significant association to older age and higher BMI. These

unexpected results likely arose due to outliers in the data (e.g., whereas the modal sleep latency value was 0, one relatively young person had a sleep latency of 10 minutes, and the only two healthy controls who had a sleep latency of greater than 0 had two of the lowest BMI values). The secondary analyses also suggested that better FTT performance was associated with higher age among healthy control participants. This result did not arise because of outliers in the data, and we cannot explain it on a physiological basis. In patients with AD, the analyses suggested that, higher education and IQ was associated with better learning and memory retention on declarative memory tasks, and better FTT performance. These results are unsurprising given the well-documented positive associations between education, IQ, and cognitive test performance (Diaz-Asper, Schretlen, & Pearlson, 2004; Van Hooren et al., 2007). However, our correlational analyses did not suggest that education or IQ influenced memory performance in healthy controls. Controls had significantly higher IQ compared to patients, perhaps at a level that bore no negative impact on cognitive performance.

Correlational analyses also suggested that, among patients with AD, longer disease duration was associated with impaired verbal learning. This association is consistent with the notion that prolonged exposure to hydrocortisone medication is likely to have negative effects on the structure and function of the hippocampus. The analyses also suggested that higher hydrocortisone doses were associated with longer sleep latency and poorer sleep efficiency, and that patients who took more doses per day experienced more disrupted sleep. These findings are consistent with numerous research indicating that higher-than-normal night-time cortisol levels cause sleep disruptions (Buckley & Schatzberg, 2005; Vgontzas et al., 2003). The analyses also suggested that patients who were diagnosed later in life had better sleep efficiency. Because patients diagnosed later in later have had less exposure to hydrocortisone medication, this

association is consistent with the notion that prolonged exposure to hydrocortisone medication is likely to have negative effects on the structure sleep. However, because of the small sample size, we urge caution in interpretation of these results, and note that they require replication in larger samples.

Structured psychiatric interviews suggested that two patients could be diagnosed with generalised anxiety disorder, two with agoraphobia, and one with current manic episodes. In addition, half of our patients had some form of medical condition. However, analyses suggested that the presence of comorbid conditions did not affect sleep or cognition.

Limitations

Given the relative rarity of AD, as well as our relatively restrictive eligibility criteria and the relatively onerous study demands placed on participants, our sample size was small and our study's statistical power limited. Hence, we were not able to conduct in-depth investigations of the associations between demographic/clinical variables and the various sleep and memory outcome variables, or of the interactions between, for instance, demographic/clinical variables and experimental condition. However, enforcing the eligibility criteria stringently means we can be confident that the observed data are free of potentially confounding effects such as age-related variability in sleep patterns or hormonal (oral contraceptives, hormone-replacement therapy) influences on sleep and cognition. Furthermore, even with this limited sample size, our findings corroborated the major hypotheses, and provided a foundation for further exploration of the relationship between sleep disruption and memory impairment in patients with AD.

A second limitation relates to the objective sleep measures we utilised. Although the actigraph is frequently employed in sleep research, it provides less robust data than polysomnographic measurements, and it does not generate measurements of sleep architecture

(i.e., the relative proportions of different sleep stages, and neurophysiological activity during those stages). Because the sequence of sleep stages, and the efficiency of transition between them, has important implications for memory consolidation (Ellenbogen et al., 2006), measuring sleep architecture via polysomnography might benefit future investigations in this field.

A third limitation relates to cortisol concentrations and their influence on sleep and cognition. For instance, food and caffeine intake, smoking, intense exercise, and encountering stressful situations may all influence cortisol levels, sleep, and cognitive performance (King & Hegadoren, 2002). Unfortunately, we did not ask participants to refrain from such intake of food or caffeine, or to avoid exercise or stressful situations, prior to entering the experimental protocol (none of the participants were smokers). Hence, a weakness of the current design is a lack of control for these potentially confounding factors. Relatedly, numerous studies have shown that a certain level of circulating cortisol is needed to enhance cognitive functioning, with decreases below or increases beyond the threshold of optimal functioning impairing cognition (McEwen & Magarinos, 1997). Therefore, the variable sub-and supra-physiological concentrations of cortisol experienced by patients with AD could play an important role in cognitive impairment that is often characteristic of these patients. The relationship between cortisol levels and memory is made even more complex by the fact that cortisol secretion follows a circadian rhythm, with cortisol levels highest in the morning and then decreasing over the course of the day (Young et al., 2004). Presumably, our healthy control participants had higher cortisol levels in the morning compared to the evening, which may have influenced cognitive functioning. However, Ross et al. (2013) showed that this same pattern occurs in patients with AD on replacement therapy (i.e., their cortisol levels are higher in the morning compared to the evening). Because cortisol levels

and variations by time of day may have important implications for cognitive functioning, future studies should take repeated measures of the hormone across the day.

Summary and Future Directions

Consistent with previously published studies (many of which only used subjective measures), our data (based on objective measures) suggest that patients with AD, relative to demographically-matched healthy controls, experience more disrupted sleep and perform more poorly on tests of declarative memory. One major novel aspect of this investigation is that it is the first to show that, in patients with AD, periods of sleep do not augment memory consolidation. These results suggest that, in patients using hydrocortisone medication, memory deficits might be attributed, at least partially, to disrupted sleep patterns that interfere with optimal consolidation of previously-learned information. We note, however, that our study design cannot rule out the possibility that other factors, such as general fatigue, may contribute to the presence of memory deficits in patients with AD. Another novel aspect of this study is that it is the first to investigate procedural memory in patients with AD. Our data suggest that this form of memory does not appear to be impaired in these patients.

Regarding directions for future research, polysomnography studies are needed to comprehensively investigate sleep architecture in patients with AD. Such studies may help explain why, for instance, sleep in these patients does not enhance consolidation of previously-learned information. Finally, intervention studies and clinical trials might seek not only to confirm the association between disrupted sleep and compromised cognitive functioning in patients with AD, but also to investigate whether the same pattern of sleep and memory deficits are present in patients using slow-release hydrocortisone. If these associations are confirmed, clinicians should prioritize treatment of disrupted sleep in patients with AD.

CHAPTER SIX

STUDY 4 - Reduced Slow-Wave Sleep and Altered Diurnal Cortisol Rhythms in Patients with Addison's Disease

A version of this chapter is currently under review in the *European Journal of Endocrinology*.

This chapter differs from the article currently under review in that here I have: (1) provided more detail regarding study design, ethical considerations and measures used, (2) added an additional area under the curve analysis for cortisol concentrations, and (3) have added several additional figures not present in the manuscript under review.

Abstract

Cortisol plays a key role in initiating and maintaining different sleep stages. Patients with Addison's disease (AD) frequently report disrupted sleep, and their hydrocortisone medication regimes do not restore the natural diurnal rhythm of cortisol. However, few studies have investigated relations between sleep quality, especially as measured by polysomnographic equipment, and night-time cortisol concentrations in patients with AD. We used sleep-adapted EEG to monitor a full night of sleep in 7 patients with AD and 7 healthy controls. We sampled salivary cortisol before bedtime, at midnight, upon awakening, and at 30-minutes post-waking. Controls had lower cortisol concentrations than patients before bedtime and at midnight. During the second half of the night, patient cortisol concentrations declined steeply, while control concentrations increased steadily. Whereas most controls experienced a positive cortisol awakening response, all patients experienced a decrease in cortisol concentrations from waking to 30-minutes post-waking ($p = .003$). Patients experienced significantly lower proportions of slow-wave sleep (SWS; $p = .001$), which was associated with elevated night-time cortisol concentrations. Overall, these results suggest that patients with AD demonstrate different patterns of night-time cortisol concentrations to healthy controls, and that relatively elevated concentrations are associated with a reduction of SWS. These hormonal and sleep architectural aberrations may disrupt the routine sleep-dependent processes of memory consolidation, and hence may explain, at least partially, the memory impairments often experienced by patients with AD.

Keywords: cortisol, hydrocortisone, diurnal rhythm, slow-wave sleep

Introduction

Patients with AD have low plasma cortisol and aldosterone levels alongside high ACTH levels and renin concentrations. A standard pharmacological intervention for these patients thus involves administration of a cortisol replacement (most often oral hydrocortisone or prednisone), along with an additional mineralocorticoid (e.g., fludrocortisone) to control sodium and potassium balance (Ten et al., 2001).

There are reciprocal relationships between hormone secretion and regulation of the sleep-wake cycle (McEwen & Karatsoreos, 2015; Steiger, 2003). Hormones of the HPA axis play a particularly important role in facilitating entry into, and in the timing and duration of, various sleep stages. Healthy individuals experiencing normal diurnal rhythmicity show relatively low cortisol, ACTH, and CRH concentrations during the early part of the night, along with high melatonin and GHRH concentrations. The high proportion of SWS during the early part of the night is stimulated by GHRH, via its effects on GH, and optimal cortisol levels experienced during early sleep probably enhance SWS through feedback inhibition of CRH (Buckley & Schatzberg, 2005; Perras, Marshall, Köhler, Born, & Fehm, 1999; Steiger et al., 1998; Steiger et al., 1992). In contrast, during the second half of the night CRH stimulates cortisol and inhibits GH, thus creating a physiological environment that is more conducive for entry into, and longer duration of, REM sleep (Buckley & Schatzberg, 2005; Vgontzas et al., 1997).

Standard GC replacement therapy does not restore the normal cortisol diurnal rhythm in patients with AD, resulting in alternating periods of sub- and supra-physiological concentrations. Hydrocortisone administration in the late afternoon or early evening leads to relatively elevated cortisol concentrations during the early part of the night (Ross et al., 2013), but the medication's short half-life results in cortisol deficiencies during the latter part of the night and the early morning (Harbeck et al., 2009). Given the importance of the HPA

axis in sleep regulation (Buckley & Schatzberg, 2005), high night-time cortisol during the early hours of sleep, accompanied by high night-time ACTH and CRH, may be one reason why patients with AD frequently report experiencing disrupted, unrefreshing sleep (Henry et al., 2015; Løvås et al., 2003; Øksnes et al., 2014).

However, only two published studies have examined the relationship between HPA-axis activity and objectively-measured sleep in patients with AD (García-Borreguero et al., 2000; Gillin et al., 1974b). Although findings from both studies support the notion that HPA-axis hypo- and hyperactivity in patients with AD alters sleep architecture, some methodological considerations temper any firm inferences. For instance, García-Borreguero et al. (2000) did not report on the sleep architecture of their patients under basal conditions (i.e., when treated with usual replacement medication regimen), and Gillin et al. (1974) was a small-*N* study in which patients ($n = 3$) and controls ($n = 5$) were not matched demographically (e.g., whereas patients' age range was 27-58, controls were aged <25 years).

Nonetheless, and especially in light of a sizable literature describing relationships between irregular HPA-axis activity and altered sleep architecture in both psychiatric and healthy samples (Backhaus et al., 2006; Dijk & Lockley, 2002; Wulff et al., 2010), it is plausible to suggest that hypo- or hyperactivity of that endocrinological system might play a role in explaining why patients with AD self-report, and objectively experience, poorer sleep quality and more frequent sleep disturbances than healthy controls (García-Borreguero et al., 2000; Henry, Ross, Wolf, & Thomas, 2017; Henry et al., 2015; Løvås et al., 2003).

The Current Study

Given the known associations between cortisol secretion and sleep architecture, and the limited research on sleep in patients with AD, we aimed to measure, using polysomnographic techniques, the sleep quality and architecture of patients with AD who were on immediate-release hydrocortisone replacement therapy. Because we sought to

maintain high levels of ecological validity, our design did not feature any manipulation of the patients' medication regimen; we describe possible mechanistic relations between cortisol concentrations and sleep architecture as they exist naturalistically, without any laboratory-based alteration, in this population.

We hypothesized that, compared to matched healthy controls, patients with AD, possibly due to their alternating periods of sub- and supra-physiological cortisol concentrations, will experience poorer sleep quality and disrupted sleep architecture. We also hypothesized that patients will, relative to controls, experience higher cortisol concentrations during the first half of the night, but lower concentrations during the second. Finally, we explored associations between cortisol concentrations and sleep patterns.

Methods and Materials

Study Design

This cross-sectional quasi-experimental study involved two participant groups: patients with AD and healthy controls. Each participant experienced 2 consecutive nights (the first an adaptation night) of polysomnograph-monitored sleep. On the second night, we sampled salivary cortisol four times: before bedtime (T1; at 21h30), at midnight (T2), upon awakening (T3; at 06h00), and 30 minutes post-awakening (T4; at 06h30).

Participants

Our sample was 7 adult patients with AD (recruited from the South African Addison's disease database (SAAD; Ross et al., 2010) and 7 healthy community-dwelling adults (recruited from a university community and surrounding neighborhoods). All were part of a cohort participating in a research programme investigating sleep, cognition, and quality of life in AD (Henry et al., 2017; Henry et al., 2014; Henry et al., 2015). We matched the groups on age and sex distribution (each group included 2 men and 5 women), and on level of education (all had completed high school).

To avoid sleep-confounding effects of age, psychiatric status, and hormonal variations (Kirschbaum et al., 1999; Palagini et al., 2013; Skeldon et al., 2016), we included only (a) individuals between the ages of 18 and 55 years, (b) individuals who did not evince severe depressive symptomatology, (c) women who were pre-menopausal, not pregnant, and not taking oral contraceptives. Healthy controls were required to be free of any chronic medical or psychiatric illnesses.

We confirmed our AD sample was representative of the entire SAAD cohort: A one-sample t -test detected no significant differences for total hydrocortisone dose, $t(6) = 0.18$, $p = .863$, and goodness-of-fit tests detected no significant differences in terms of race distribution, $\chi^2(3, N = 7) = 0.96$, $p = .810$, or sex distribution, $\chi^2(1, N = 7) = 0.28$, $p = .596$. There was, however, a significant difference for age, $t(6) = -3.22$, $p = .018$, which arose because of our stringent exclusion criteria. Patients in the current study were younger than those in the SAAD cohort ($M = 36.86 \pm 12.38$ versus 51.90 ± 20.84 years).

Measures

Sociodemographic questionnaire. This measure obtained information about biographic variables (e.g., age, education) and general medical history. For patients with AD, we extracted from the SAAD database information regarding type and dosage of current medication, and duration since diagnosis.

Screening instruments.

Mini International Neuropsychiatric Interview (MINI; English version 5.0.0; Sheehan et al., 1998). This brief (15-min) structured diagnostic interview elicits information regarding the presence of major DSM-IV Axis I psychiatric disorders and in this study, was used to assess current psychiatric status. We excluded individuals with any current psychiatric disorder from the healthy control group.

Beck Depression Inventory-Second Edition (BDI-II; Beck et al., 1996). The BDI-II was used to measure current (2-week) intensity, severity, and depth of depression in respondents. Individuals with BDI-II scores greater than 29 (indicating severe depression) were excluded from participation.

Subjective sleep assessment. The Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) measured self-reported sleep quality and disturbances over the month prior to completion. It comprises 19 items, each related to at least one of seven components (sleep quality, latency, duration, disturbances, and efficiency; use of sleeping medication; and daytime dysfunction due to disrupted sleep). The score on each component ranges from 0-3; hence, the total PSQI score ranges from 0-21, with higher scores representing poorer sleep quality marked by more disruptions. Individuals with a total score above 5 are considered to have poor sleep quality (Mollaveva et al., 2016).

Objective sleep assessment. We used a Nihon Kohden sleep-adapted EEG. PSGs are the standard apparatus for quantifying sleep and its associated physical phenomena, and have proven to be a reliable means of measuring sleep efficiency and total sleep time, and of classifying sleep stages (Kushida et al., 2001). Several parameters are commonly recorded by a PSG to help classify the various sleep stages. In the current study, the PSG measured brain activity, eye movements, and muscle activity as the participant entered and passed through different sleep stages. We recorded data following the International 10-20 system (Berry et al., 2012).

Cortisol. We took salivary cortisol measurements as surrogate indicators of plasma cortisol concentration, collecting samples using Sarstedt salivettes (Sarstedt, Nümbrecht, Germany). Salivary cortisol was analysed by the National Health Laboratory Services at Groote Schuur Hospital using a competitive electrochemiluminescent immunoassay on the

Roche Cobas 6000 (Roche Diagnostics GmbH, Mannheim, Germany) with a coefficient of variation of 4%.

Procedure

Research ethics committees from the University of Cape Town's Department of Psychology and Faculty of Health Sciences, both of which adhere to the Declaration of Helsinki (World Medical Association, 2013), approved the study procedures. All participants gave informed consent for collection, use, and reporting of their data after being explained the full purpose of the study. No participant reported experiencing adverse events during the course of the study procedures. All data are held confidential, and participants' rights to anonymity and privacy were guaranteed and have been sustained.

We instructed those in the AD group to continue taking their hydrocortisone medication at their usual time, and obtained verbal confirmation that they did so. All testing took place at a dedicated sleep laboratory. Sleep architecture was recorded in a sound-attenuated, light- and temperature-controlled room for 2 consecutive nights. The first of these was an adaptation night, which allowed participants to acclimatize to a new sleeping environment (Kushida et al., 2001). Following precedent (Markovic, Achermann, Rusterholz, & Tarokh, 2018; Roehrs & Roth, 2018; Sprajcer et al., 2018), data from this night were not analyzed.

Each participant arrived at the hospital at 20h30 on the adaptation night (see Figure 14). After reading and signing informed consent documents, they completed the PSQI, and were then attached to the PSG. At 22h00, lights were turned off and they were instructed to lie down and fall asleep as soon as possible. Lights were turned on at 06h00. Before leaving the laboratory, participants were instructed not to consume any caffeinated drinks during the day and to have their last meal 2-3 hours before bedtime.

Participants returned to the sleep laboratory later that day, at around 20h00 for the experimental night (see Figure 15). The subsequent protocol was identical to that of the adaptation night, except that we sampled salivary cortisol four times: the first (T1) shortly before bedtime, at 21h30; the second (T2) at midnight (participants were woken briefly); the third (T3) upon awakening, at approximately 06h00; and the fourth (T4) 30-minutes post-awakening, at approximately 06h30. Upon completion of these procedures, participants were debriefed and compensated.

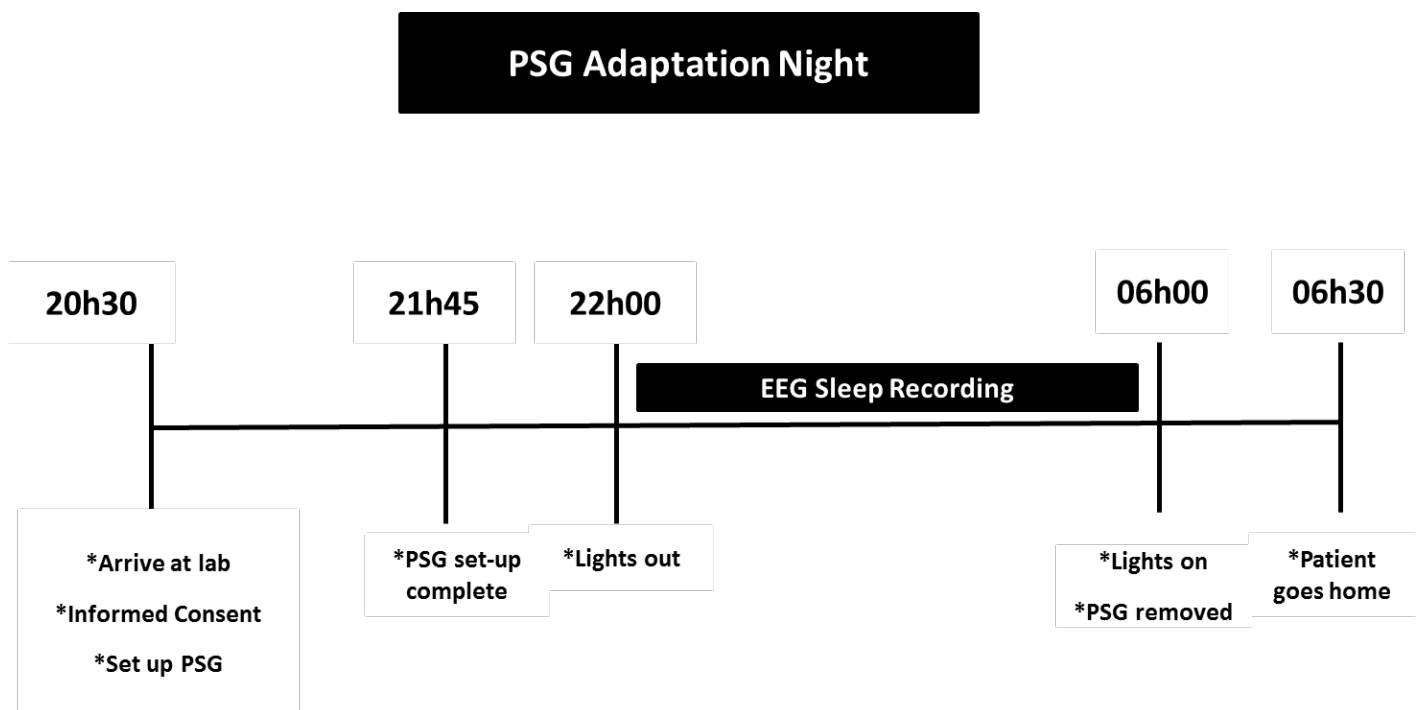


Figure 14. Study procedure during the adaptation night.

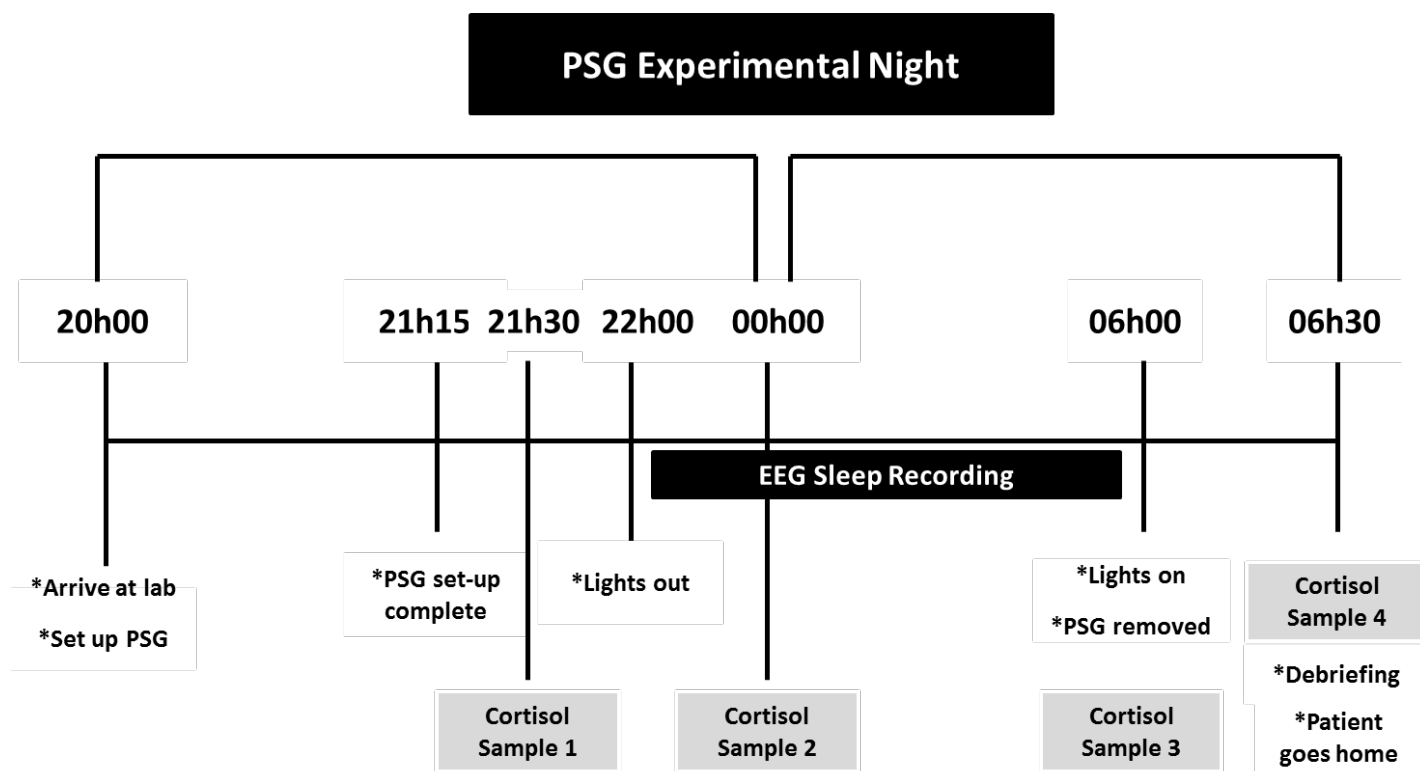


Figure 15. Study procedure during the experimental night.

Data Management and Statistical Analyses

Subjective sleep. We used PSQI total score to represent overall self-reported sleep quality, and calculated the proportion of participants within each group who could be classified as poor sleepers (i.e., with total score > 5). We also used individual PSQI items to estimate four other subjective sleep outcome variables: total sleep time (in minutes), number of minutes spent awake after sleep onset, sleep efficiency (proportion of time in bed spent asleep), and sleep latency (length of time, in minutes, between going to bed and falling asleep).

Objective sleep. On the experimental night, each participant was evaluated continuously for approximately 8 hours. We examined, for the full night and by half segments of the night, these 13 sleep-related outcome variables: sleep efficiency (proportion of time in bed spent asleep); sleep latency (length of time, in minutes, between lights out and falling asleep); REM latency (length of time, in minutes between lights out and onset of the

first REM cycle); wake after sleep onset (WASO; the number of minutes spent awake in the period between sleep onset and final waking); time and proportion spent in each stage of sleep (N1, N2, SWS and REM); and number of awakenings (number of times the participant awoke for more than 1 minute in the period between sleep onset and final waking).

All of these outcome variables were examined for the full night (the 8-hr recording), and by half segments of the night (except Sleep and REM latencies, which were only examined during the first half of the night). To ensure consistency in the calculation of half segments of the night, for each participant we divided the period between sleep onset and final waking into two equal portions.

We analyzed sleep data using Polysmith analysis software (Rosbach, Germany), and scored them according to standardized criteria outlined in the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events (Berry et al., 2012). Sleep records were scored by M.H. and an independent qualified sleep technician, both of whom were blind to experimental group assignment. For sleep stage analysis, the two scorers had an epoch-by-epoch agreement of 95%.

Measuring cortisol levels and deriving outcome variables. We used values from T1 (i.e., sample taken at 21h30), T2 (00h00), T3 (06h00), and T4 (06h30) to derive another three outcome variables: change in cortisol concentration during the first half of the night ($\Delta\text{CortFirst}$; T2 - T1); change during the second half of the night ($\Delta\text{CortSecond}$; T3 - T2); and cortisol awakening response (CAR; T4 - T3).

We calculated, for descriptive purposes only, an area under the curve (AUC) measure. For this calculation, we used the composite trapezoidal rule to compute AUC for the first and second halves of the night ($\text{AUC}_{21\text{h}30 - 00\text{h}00}$ and $\text{AUC}_{00\text{h}00 - 06\text{h}00}$, respectively), and for the CAR ($\text{AUC}_{06\text{h}00-06\text{h}30}$).

Power analysis and sample selection. An a priori power analysis suggested that the sample size be set at $N = 90$ ($n = 45$ per group) if we wanted to achieve statistical power of at least .95 using a cross-sectional matched-participant design investigating between-group differences (parameters: effect size = medium-large, Cohen's $d = 0.70$; $\alpha = .05$; Erdfelder et al., 1996). We chose a medium-large effect size parameter because the only published investigation of baseline sleep architecture in AD patients (Gillin et al., 1974b) reported an average Cohen's d of 0.72 across all measured sleep variables. However, given the rarity of AD, both globally and in South Africa (there are fewer than 200 patients in the SAAD database), along with our stringent eligibility criteria (e.g., fewer than 50 of the patients in the SAAD database met our age-related inclusion criterion), we could only enrol 7 patients (and hence $N = 14$). This sample size generated statistical power of .34.

Descriptive and inferential statistical analyses. We completed all analyses using SPSS version 24 and R version 3.4.3, with the threshold for statistical significance (α) set at 0.05 unless noted otherwise. Given the small N and non-normal distribution of outcome variables, we used a non-parametric statistical test (the Mann-Whitney U test) to conduct between-group comparisons for (a) sociodemographic characteristics, (b) PSQI total score, (c) PSG-measured sleep quality and architecture for both the whole-night and split-night datasets, and (c) cortisol-related variables. We conducted a Fisher's Exact test to determine the magnitude of association between group (AD vs Control) and proportion of individuals classified as poor sleepers (PSQI total score > 5). A series of Wilcoxon signed rank tests compared subjective and objective measures of total sleep time, WASO, sleep efficiency, and sleep latency. Because of our small N , we used scatter plots to describe associations between (a) sleep variables and cortisol concentrations, and (b) patient disease characteristics and sleep variables / cortisol concentrations.

Results

Sample Characteristics

By design, there were no significant between-group differences in terms of age ($p = .654$), or education ($p = .165$; Table 12). Analyses also detected no significant between-group BMI differences ($p = .257$).

Table 12
Overall Sample Characteristics (N = 14), and Patient Clinical Characteristics (n = 7)

Variable	Addison's Disease (n = 7)	Healthy Controls (n = 7)	U	p	ESE
Age	40 (23-44) 20-55	44 (21-50) 20-50	21	.654	0.12
Education	15 (12-16) 12-18	12 (12-15) 12-15	14.5	.165	0.37
Body mass index ^a	25.64 (21.13-34.89) ^e 20.05-37.55	23.24 (20.20-25.43) 19.26-26.37	8	.257	0.34
Age at diagnosis (years) ^b	25.83 (16.27) 7 - 54	-	-	-	-
Duration of AD (years) ^b	10.00 (4.82) 1 - 14	-	-	-	-
Total hydrocortisone dose	23.57 (6.90) 15 - 35	-	-	-	-
Hydrocortisone (mg/kg) ^c	0.30 (0.10) 0.18 - 0.46	-	-	-	-
Number of doses per day	2.29 (0.49) 2 - 3	-	-	-	-
Fludrocortisone dose (mg) ^d	0.14 (0.38) 0.10 - 0.50	-	-	-	-

For the variables age, education and BMI, medians (with IQR in parentheses) are presented on the top line, and range is presented below that. For clinical characteristics, means (with standard deviations in parentheses) are presented on the top line, and range is presented below that. ESE = effect size estimate (in this case, r for Mann-Whitney U tests).

^aCalculated by dividing the participant's weight by height² (information obtained from the sociodemographic questionnaire). ^bData based on 6 patients (1 patient did not provide the requisite information). ^cData based on 6 patients (1 patient did not provide weight-related information). ^dData based on 5 patients (2 patients were not prescribed this medication).

^eData based on 4 participants (2 patients did not provide details of their height, and 1 did not provide details of her weight).

Patient Clinical Data

Two patients had hypothyroidism and one had diabetes. Structured psychiatric interviews suggested one could be diagnosed with generalised anxiety disorder, agoraphobia, and current manic episodes, and another two with generalised anxiety disorder. Tables 12 and 13 present further details regarding these characteristics, as well as individual regimens of immediate-release hydrocortisone.

Table 13

Patient Medication Regimen (N = 7)

Patient Number	Total Dose (mg)	Dose 1 (Time)	Dose 2 (Time)	Dose 3 (Time)
1	15	10 (08h00)	5 (14h00)	----
2	20	10 (06h30)	5 (11h30)	5 (16h00)
3	20	15 (06h00)	5 (17h00)	----
4	20	10 (07h00)	10 (21h00)	----
5	25	15 (06h00)	5 (12h00)	5 (16h00)
6	30	20 (07h00)	10 (16h00)	----
7	35	25 (07h00)	10 (16h00)	----

Between-group Comparisons: Subjective Sleep Data

A larger proportion of patients than controls were classified as poor sleepers: four patients (57.1%) and two controls (28.6%) self-reported a PSQI total score > 5 , $p = .296$, $V = 0.29$. On average, patients reported poorer sleep quality (i.e., obtained higher PSQI total scores) than controls: AD: Median (IQR) = 6 (3-8) vs Control: Median (IQR) = 3 (2-6), $U = 15.5$, $p = .242$, $r = 0.31$.

Between-group Comparisons: Objective Sleep Data

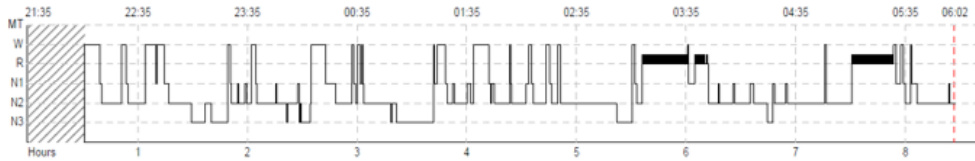
Several extreme outliers (> 3 SDs from the mean) were present in the data (seven related to sleep outcome variables, two to cortisol outcome variables, and one to patient timing of last daily dose; see Appendix J: Supplementary Figure 1). Results of analyses described below are reported with and without outliers.

On average, all participants slept for between 6.5 and 7 hours (patients with AD: $M = 412.83$ mins, $SD = 19.17$; controls: $M = 398.58$ mins, $SD = 40.33$). Figures 16 and 17 present separate hypnograms for each patient and control, respectively. As can be seen, both patients and controls displayed the typical cyclical nature of sleep, with more SWS during the first half of the night and more REM sleep during the second half of the night (Figures 18-20). Of note is that the patient who took her last hydrocortisone dose latest in the day had the longest sleep latency (taking over an hour to fall asleep) and the shortest REM latency (less than 50 minutes). For all participants, the brief awakenings at T2 had no detectable effect on sleep EEG.

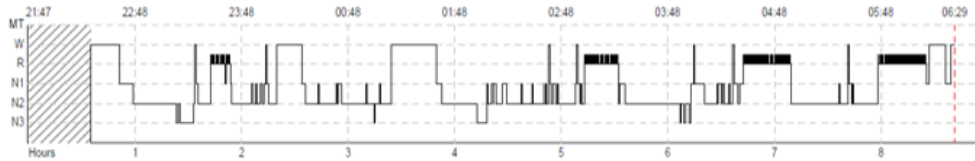
Results of between-group analyses are depicted in Table 14. Across the whole night and during the first half of the night, patients with AD experienced, on average, significantly less SWS than controls (see Figures 18-20). Analyses detected no significant between-group differences for measures pertaining to the second half of the night (all $ps > .055$). This pattern of results remained almost identical when data sets containing extreme outliers were removed from the analysis. The one exception here was that, in the outlier-free analysis, patients with AD had significantly more N2 sleep during the first half of the night than controls.

Within both groups, subjective sleep reports (for past-month sleep) were consistent with objective PSG-measured sleep on the experimental night (i.e., the analyses detected no significant between-measure differences; see Table 15).

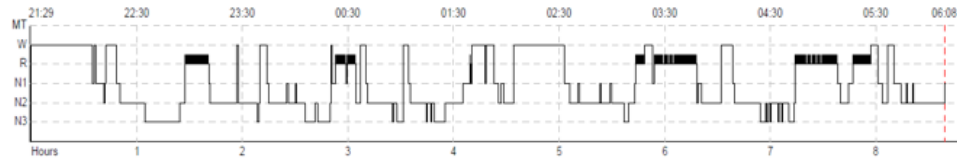
**Patient 1 - Total HC dose: 15mg
Time last dose: 14h00**



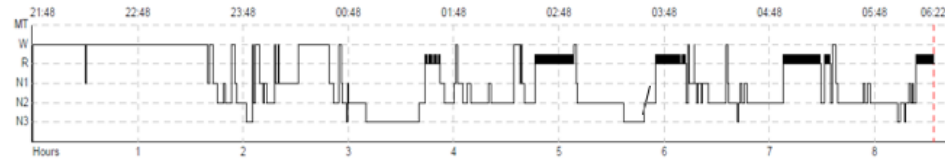
**Patient 2 - Total HC dose: 20mg
Time last dose: 16h00**



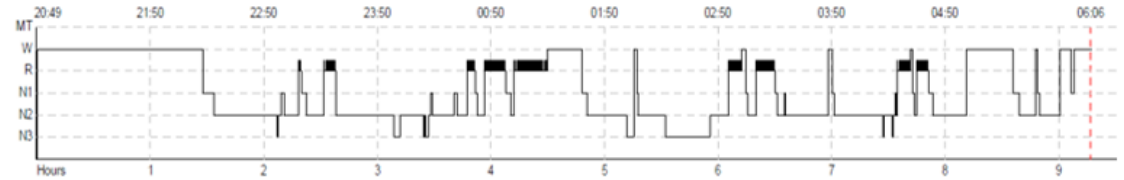
**Patient 3 - Total HC dose: 20mg
Time last dose: 17h00**



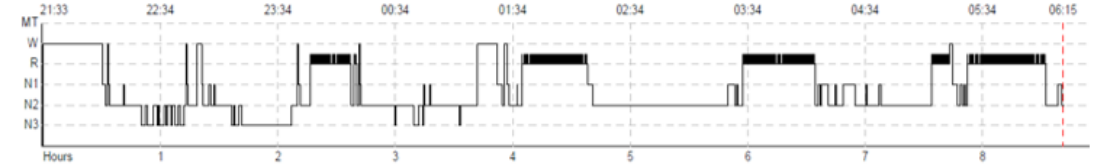
**Patient 7 - Total HC dose: 35mg
Time last dose: 16h00**



**Patient 4 - Total HC dose: 20mg
Time last dose: 21h00**



**Patient 5 - Total HC dose: 25mg
Time last dose: 16h00**



**Patient 6 - Total HC dose: 30mg
Time last dose: 16h00**

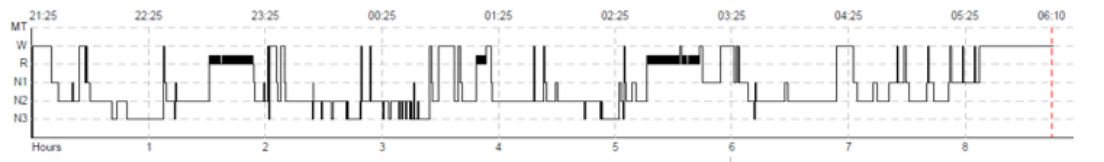


Figure 16. Hypnograms illustrating the architectural distribution of sleep for each patient.

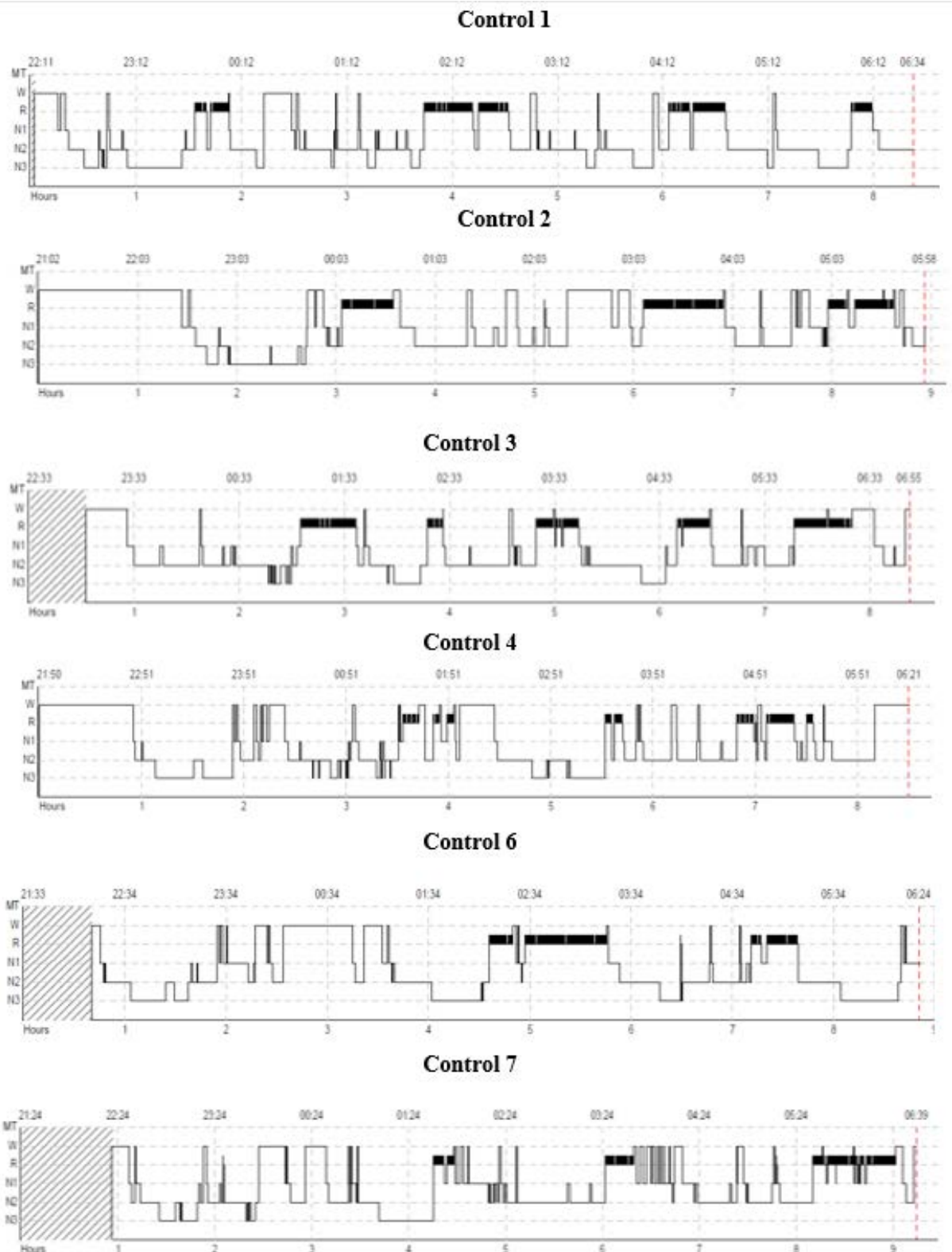


Figure 17. Hypnograms illustrating the architectural distribution of sleep for each control. A hypnogram could not be produced for one control participant (due to technical errors, this participants sleep data was recorded across three different files which could not be merged).

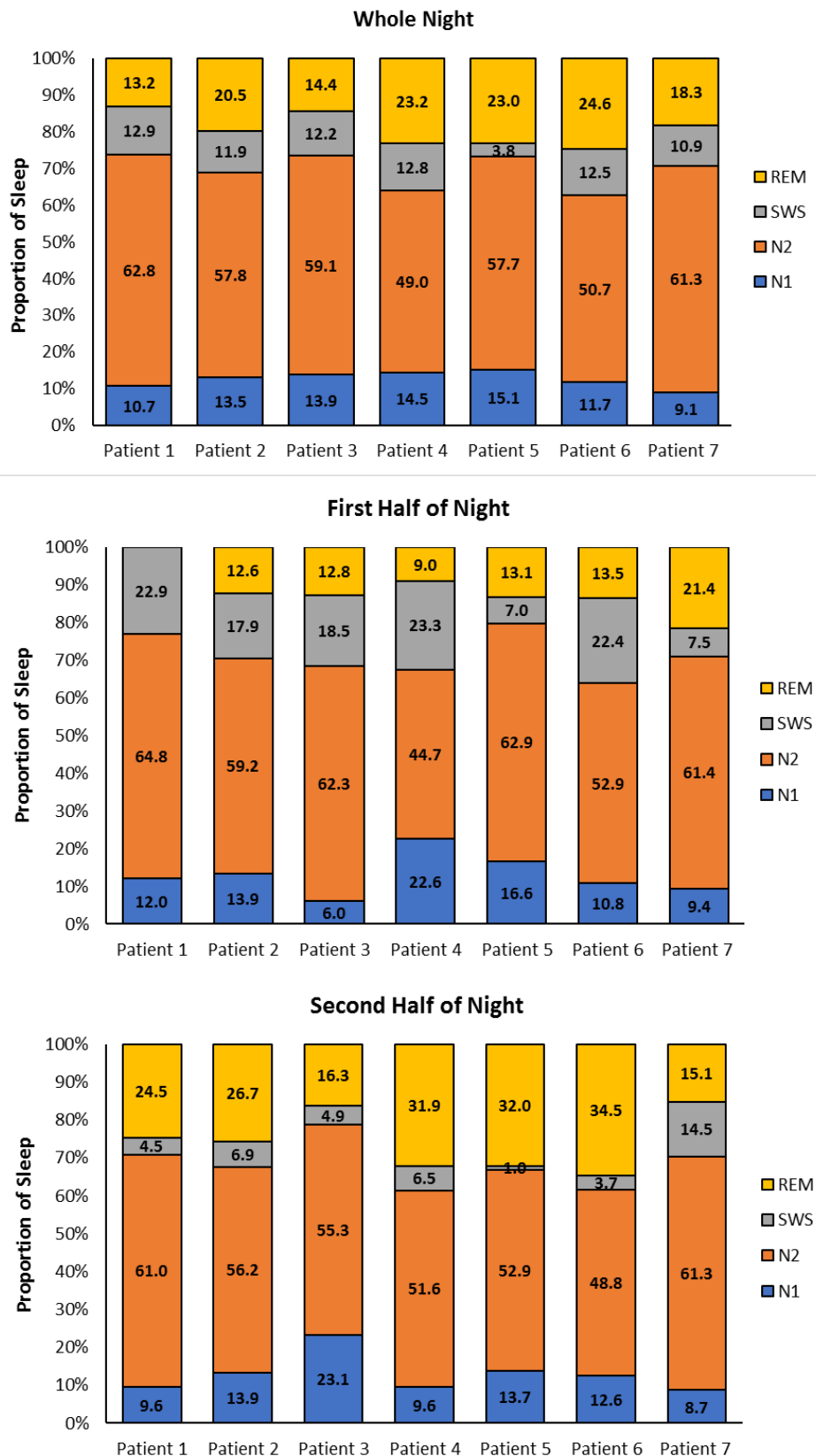


Figure 18. Distribution of sleep stages across the whole night, first half of the night, and second half of the night for each patient.

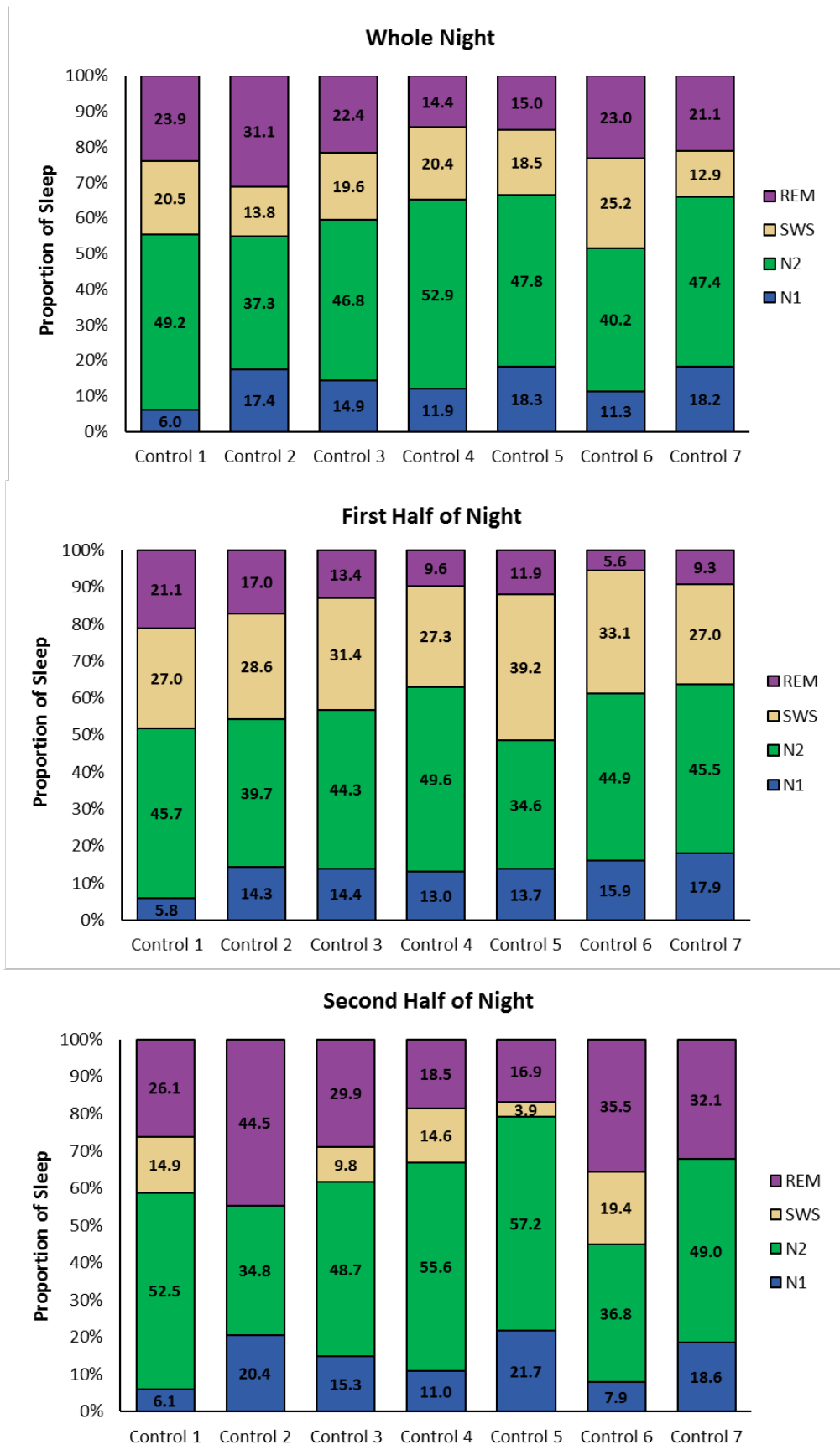


Figure 19. Distribution of sleep stages across the whole night, first half of the night, and second half of the night for each control.

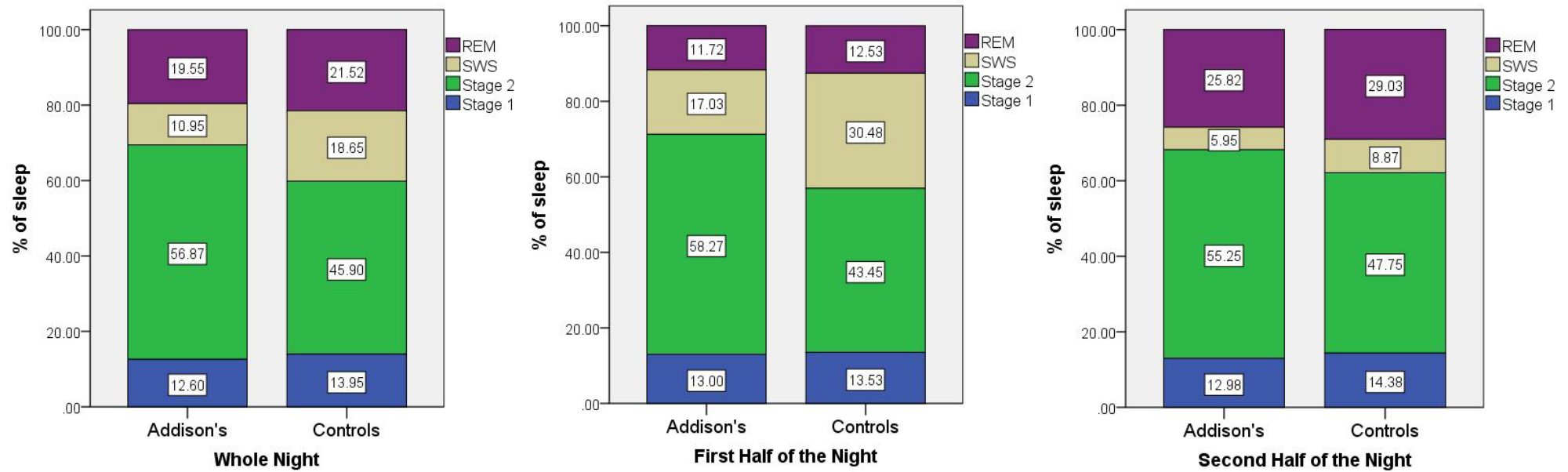


Figure 20. Distribution of sleep stages across the whole night, first half of the night, and second half of the night.

Table 14

Objective sleep quality and architecture in patients and controls (N = 14)

Variable	Addison's Disease (<i>n</i> = 7)	Healthy Controls (<i>n</i> = 7)	<i>U</i>	<i>p</i>	ESE
	Median (IQR)	Median (IQR)			
Whole night					
Sleep Efficiency	82.52 (81.9-87.15)	83.47 (79.37-87.4)	23	.424	0.01
Sleep Latency	20.85 (8.35-26.9)	15.85 (10.35-32.35)	22	.375	0.09
REM Latency	51.35 (49.85-96.82)	142.82 (82.35-206.35)	11	.042*	0.46
WASO	57.73 (37.85-65.35)	65.85 (51.35-72.35)	17	.169	0.26
N1 Time	52.98 (44.85-59.85)	55.98 (45.85-66.85)	20	.283	0.15
N2 Time	247.35 (212.85-252.85)	185.32 (163.35-206.85)	4	.005*	0.70
SWS Time	48.85 (44.35-52.85)	75.82 (56.35-93.35)	1.5	.002**	0.79
REM Time	81.48 (61.85-99.85)	92.35 (55.35-108.35)	20.5	.305	0.14
N1%	13.5 (10.65-14.45)	14.85 (11.25-18.15)	17	.169	0.26
N2%	57.77 (50.65-61.25)	47.35 (40.15-49.15)	3	.004*	0.73
SWS%	12.15 (10.85-12.75)	19.55 (13.75-20.45)	0.5	.001**	0.82
REM%	20.45 (14.35-23.15)	22.42 (14.95-23.85)	20	.282	0.15
Awakenings	9.07 (5.85-10.85)	8.85 (6.85-10.07)	21.5	.350	0.10
First half of the night					
Sleep Efficiency	79.5 (77.5-83.9)	76.2 (70.9-83.6)	15.5	.125	0.31
WASO	26.4 (22.9-30.9)	29.9 (23.9-43.9)	17.5	.185	0.24
N1 Time	22.9 (19.4-32.4)	25.4 (19.4-27.9)	22	.375	0.09
N2 Time	122.9 (104.9-128.4)	80.9 (73.4-94.9)	6	.009*	0.63
SWS Time	33.4 (15.4-43.4)	55.7 (52.9-57.4)	< 0.1	.001**	0.84
REM Time	26.9 (12.9-29.4)	19.4 (16.9-31.4)	22	.375	0.09
N1%	12 (9.4-16.6)	14.3 (13-15.9)	20	.283	0.15
N2%	61.4 (52.9-62.9)	44.9 (39.7-45.7)	4	.005*	0.70
SWS%	18.5 (7.5-22.9)	28.6 (27-33.1)	< 0.1	.001**	0.89
REM%	12.8 (9-13.5)	11.9 (9.3-17)	24	.475	0.02
Awakenings	5.2 (2.9-5.9)	4.9 (3.9-5.7)	247	.474	0.02
Second half of the					
Sleep Efficiency	89.1 (81.2-94.8)	90.6 (82.84-95.86)	21	.328	0.12
WASO	30.5 (11.9-45.4)	25.7 (9.85-40.85)	20	.283	0.15
N1 Time	27.9 (21.9-31.4)	31.5 (18.85-42.35)	22	.375	0.09
N2 Time	120.9 (109.9-121.9)	111.35 (87.85-115.35)	12	.055	0.43
SWS Time	10.4 (8.4-15.4)	21.1 (0-35.85)	21	.327	0.12
REM Time	58.1 (32.4-75.4)	64.5 (38.35-84.5)	19	.241	0.19
N1%	12.6 (9.6-13.9)	15.3 (7.9-20.4)	22	.375	0.09
N2%	55.3 (51.6-61)	49 (36.8-55.6)	12	.055	0.43
SWS%	4.9 (3.7-6.9)	9.8 (0-14.9)	20	.283	0.15
REM%	26.7 (16.3-32)	29.9 (18.5-35.5)	18	.203	0.22
Awakenings	4.7 (2.9-4.9)	2.85 (1.85-4.85)	17	.167	0.26

Note. ESE = effect size estimate (in this case, r); WASO = wake after sleep onset.

* $p < .05$. ** $p < .004$ (statistically significant after the Bonferroni correction).

Table 15

Comparison of Subjective and Objective Sleep Measures in Patients and Controls (N = 14)

Variable	Addison's disease (n = 7)					Control (n = 7)				
	PSQI	PSG	z	p	ESE	PSQI	PSG	z	p	ESE
	Median (IQR)	Median (IQR)				Median (IQR)	Median (IQR)			
TST (h)	7 (7-7.5)	6.93 (6.71-7.12)	-0.34	.735	0.09	7 (6.5-8)	6.59 (6.37-7.26)	-0.34	.735	0.09
WASO (min)	42 (30-90)	57.73 (37.85-65.35)	-0.85	.398	0.23	35 (0-50)	65.85 (51.35-72.35)	-1.86	.063	0.50
Latency (min)	10 (5-30)	20.85 (8.35-26.90)	-0.68	.499	0.18	10 (4-15)	15.85 (10.35-32.35)	-1.86	.063	0.50
Efficiency (%)	90.32 (70-96.77)	82.52 (81.90-87.15)	-0.68	.499	0.18	86.67 (80-89)	83.47 (79.37-87.40)	-0.68	.499	0.18

Note. TST = total sleep time; WASO = wake after sleep onset; ESE = effect size estimate (in this case, r for Wilcoxon signed rank tests).

Between-group Comparisons: Cortisol Concentrations

Analyses detected significant between-group differences at T4 (patients had significantly lower cortisol levels 30-minutes post-awakening), and for CAR (Table 16). Of note regarding the latter is that 5 of the 6 control participants for whom the variable could be calculated experienced a positive CAR, whereas none of the patients did. Furthermore, whereas controls experienced an increase in cortisol levels during the second half of the night, patients experienced a decrease (Figure 21). This pattern of results held when extreme outliers were removed from the data.

The pattern of cortisol concentrations was relatively homogenous for controls, but more variable for patients (Figure 22). Of note is that, compared to all other patients, Patient 4 (i.e., the individual who took her last hydrocortisone dose latest in the day) had a substantially higher cortisol concentration at bedtime, and experienced the biggest decline in concentrations during the second half of the night.

Table 16
Cortisol Concentrations in Patients and Controls (N = 14)

Variable	Addison's Disease (n = 7)	Healthy Controls (n = 7)	U	p	ESE
	Median (IQR)	Median (IQR)			
T1	8.02 (5.91 – 10.29)	5.28 (4.58 – 6.26) ^b	5	.011*	0.64
T2	13.98 (11.01 – 20.29)	7.30 (6.67 – 8.73) ^c	1	.007*	0.74
T3	12.62 (7.22 – 16.14) ^a	12.32 (10.99 – 20.24) ^d	12	.169	0.28
T4	6.70 (4.32 – 10.41)	21.67 (14.37 – 25.58)	4	.002**	0.77
ΔCortFirst	5.49 (1.37 – 11.92)	2.41 (0.74 – 4.15) ^c	7	.093	0.40
ΔCortSecond	-1.45 (-6.27 – 2.90) ^a	5.50 (3.71 – 7.53) ^c	1	.009*	0.74
CAR	-5.00 (-8.75 – -2.50)	3.50 (2.00 – 8.25) ^d	0.5	.003**	0.78

Note. ESE = effect size estimate (in this case, r for Mann-Whitney U tests); CAR = cortisol awakening response.

^aData based on 6 participants (1 sample returned as insufficient for analysis).

^bData based on 6 participants (1 sample returned as insufficient for analysis).

^cData based on 4 participants (2 samples returned as insufficient for analysis; 1 sample was not obtained due to researcher error).

^dData based on 6 participants (1 sample returned as insufficient for analysis).

* $p < .05$. ** $p < .007$ (statistically significant after the Bonferroni correction).

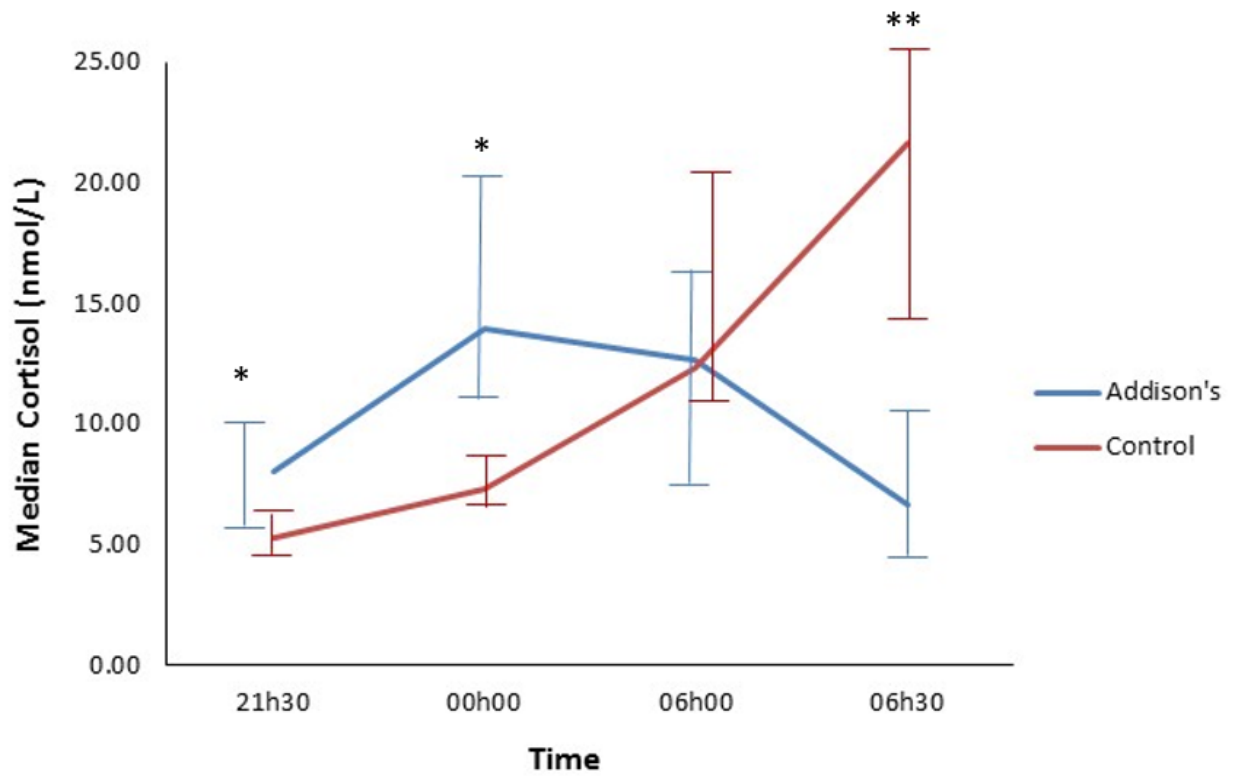


Figure 21. Changes in cortisol levels across the night and morning (error bars represent Inter-quartile range).

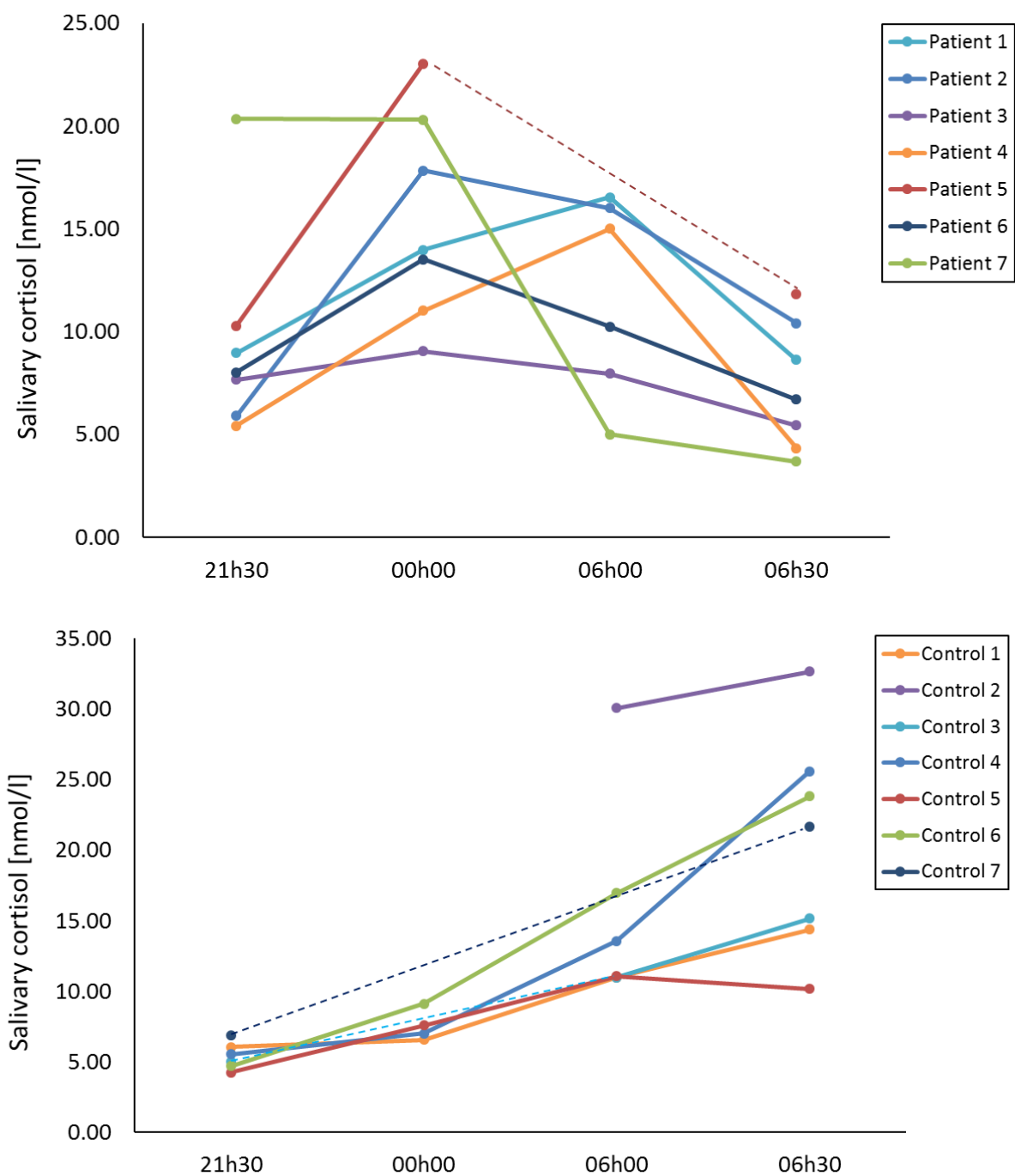


Figure 22. Changes in cortisol levels across the night and morning for each patient (top) and control (bottom). Data for one patient and three controls were not available at various time points - their graphs have dashed lines representing the potential trend in cortisol level changes (except for Control 2 who is missing the first two cortisol measurements and therefore a trend estimation cannot be made).

Regarding AUC data, patients had a higher median salivary cortisol AUC during the first half of the night (AD: 1720.50 nmol.min/l, IQR = 1253.25-2498.25; Controls: 943.13 nmol.min/l, IQR = 900.94-1012.88) and during the second half of the night (AD: 4617 nmol.min/l, IQR = 3972.60-5640.30; Controls: 3529.80 nmol.min/l, IQR = 3207.17-4445.10). However, controls had a higher median salivary cortisol AUC during the CAR period (Controls: 489.75 nmol.min/l, IQR = 364.80-693.94; AD: 271.95 nmol.min/l, IQR = 183.49-381.90).

Correlations: Sleep and Cortisol

We described associations, within each group separately, between sleep in each half of the night and specific cortisol values. Because three controls had missing cortisol values at midnight, we do not describe relationships of sleep outcomes with cortisol values at midnight, or with $\Delta\text{CortFirst}$ and $\Delta\text{CortSecond}$, in this group.

Sleep during the first half the night and cortisol concentrations. Here, we describe associations between PSG outcome variables, taken during the first half of the night, and three cortisol outcome variables: (a) the measure taken at bedtime, (b) the measure taken at midnight, and (c) $\Delta\text{CortFirst}$. Within the AD group, patients with higher cortisol concentrations at bedtime had fewer awakenings, and patients with higher cortisol levels at midnight had less SWS (see Appendix J: Supplementary Figure 2). When outliers were removed, only the association between cortisol levels at midnight and SWS remained.

Within the healthy control group, those with higher cortisol concentrations at bedtime had shorter REM latencies, better sleep efficiency, and less SWS (see Appendix J: Supplementary Figure 2). Generally, this pattern of results held when outliers were removed; the only exception was that cortisol levels at bedtime and sleep efficiency were no longer associated.

Sleep during the second half the night and cortisol concentrations. Here, we described associations between PSG outcome variables, taken during the second half the night, and three cortisol outcome variables: (a) the measure taken at midnight, (b) the measure taken upon awakening, and (c) $\Delta\text{CortSecond}$. Within the AD group, patients with higher cortisol concentrations at waking had better sleep efficiency, and those who had larger decreases during the second half of the night experienced more SWS (see Appendix J: Supplementary Figures 3 and 4). When outliers were removed, only the association between cortisol levels upon awakening and sleep efficiency remained.

Within the healthy control group, those with higher cortisol concentrations at waking had more REM sleep (see Appendix J: Supplementary Figure 3). This association remained after outliers were removed.

Correlations: Patient Disease Characteristics, Whole-night Sleep, and Cortisol

Because nearly all patients took two doses of hydrocortisone medication per day (bar two patients who took three doses/day), we did not examine relationships between number of doses and sleep/cortisol variables. Patients with a higher total hydrocortisone dose had poorer sleep efficiency, and those with a higher dose/kg had longer sleep latencies and less N2% (see Appendix J: Supplementary Figure 5). Patients who took their last dose of medication later in the day had less SWS%, higher cortisol levels at bedtime, and a larger decrease in cortisol during the second half of the night (see Appendix J: Supplementary Figure 6). When outliers were removed, only the association between dose/kg and N2% remained, however.

Duration of AD appeared to bear no substantial association to any sleep or cortisol outcome variable (see Appendix J: Supplementary Figure 6).

Discussion

Several studies document self-reported disturbances of sleep quality in patients with AD, but few have used polysomnographic measures to confirm these disruptions. The current study aimed to quantify sleep quality and architecture of patients with AD, and to explore the role of cortisol concentrations in altered sleep patterns. Our patient group exhibited altered sleep architecture (specifically, reduced SWS), which was associated with elevated night-time cortisol concentrations.

Our results are consistent with the only other study in the AD literature that reports on PSG-measured sleep when replacement medication is administered as usual (Gillin et al., 1974b). Across the two studies, patients spent similar proportions of time in Stage 2 sleep (63% in the current study versus 57% in Gillin et al. (1974)), in SWS (14% versus 11%), and in REM sleep (19% versus 20%). Moreover, in that study, as in ours, patients exhibited similar sleep quality and architecture to healthy controls, aside from SWS disruptions. As noted earlier, however, Gillin et al. (1974) did not include matched samples of patients and controls.

SWS plays a critical role in the general physiological restorative function of sleep and in specific cognitive processes such as memory consolidation (Diekelmann & Born, 2010; Luyster et al., 2012). Hence, disrupted sleep and altered circadian rhythms lead to energy imbalances, fatigue, memory deficits, and poorer quality of life (Depner et al., 2014; Zhi et al., 2016). Therefore, it is likely that when patients with AD experience decreased SWS they will also experience these negative health outcomes. Indeed, fatigue and memory deficits are features of adrenal failure that persist despite replacement therapy, and are major contributors to self-reported impaired health in AD (Henry et al., 2017; Løvås & Husebye, 2003).

Regarding between-group differences in night-time cortisol concentrations, patients had higher cortisol levels prior to sleep onset and during the first half of the night, but cortisol deficiencies during the second half of the night. The most marked between-group difference occurred after waking: Whereas most controls experienced a positive CAR, no patient did. These data are consistent with previous reports suggesting that, despite GC replacement therapy, patients with AD experience alterations of normal cortisol diurnal rhythms (Johannsson et al., 2015). Moreover, the observed trends during the latter part of the night and early morning are consistent with previous literature reporting on cortisol secretory action in patients with AD (Harbeck et al., 2009). Because cortisol plays a vital role in ensuring smooth transitions between sleep stages (Bennion et al., 2015), irregular patterns of secretion in patients with AD might explain their altered sleep architecture.

Consistent with this conjecture, between-group differences in sleep architecture and in cortisol concentrations both occurred during the first half of the night, and our scatter plot analyses confirmed associations between levels of the hormone and discrete sleep parameters. For instance, within the AD group, higher cortisol concentrations at midnight were associated with less SWS, whereas lower cortisol concentrations during the second half of the night were associated with more SWS. These results are consistent with a substantial body of research indicating that high cortisol concentrations during the first half of the night (as exhibited by our patient group) are associated with less SWS (also exhibited by our patient group; i.e., lower cortisol levels facilitate the initiation and maintenance of SWS; Gillin et al., 1974b; Steiger, 2003). Similarly, controls who had higher cortisol concentrations at bedtime had less SWS. Within the control group, higher cortisol concentrations at bedtime were associated with shorter REM latency, a finding consistent with research indicating that higher cortisol levels facilitate

entry into REM sleep (Antonićević & Steiger, 2003; García-Borreguero et al., 2000; Vgontzas et al., 1997).

In the current sample, some disease and medication characteristics of patients with AD were associated with sleep parameters and night-time cortisol secretion. Patients who took larger doses of hydrocortisone had poorer sleep efficiency, shorter sleep latency, and less Stage 2 sleep. This result is understandable given that larger doses should translate into higher cortisol concentrations, and high cortisol concentrations increase both sleep onset latency and number of awakenings after sleep onset (Steiger, 2003). Patients who took their last dose of hydrocortisone later in the day had higher cortisol concentrations at bedtime and less SWS, further supporting the notion that low cortisol levels are needed to facilitate the initiation and maintenance of SWS.

Limitations and Future Directions

Measurement and sample size issues limit the strength of the conclusions we can draw from the current data. The fact that we took only four saliva samples from bedtime through waking means we are limited in making inferences about how subtle changes in nocturnal cortisol secretory patterns, particularly between midnight and early morning when REM sleep predominates, may influence sleep parameters. Future studies might test the proposition that SWS is more sensitive to cortisol alterations than REM.

Furthermore, although cortisol measurement by saliva has numerous advantages over that by plasma (e.g., stress-free sampling, lower costs, and non-invasive collection methods; Del Corral et al., 2016), salivary cortisol measured by radioimmunoassay has intrinsic problems of variability. In the current sample, for instance, concentrations may have been influenced by contamination of saliva with hydrocortisone tablets (and may explain, for instance, why patients experienced increasing cortisol concentrations between 21h30 and midnight, despite taking their

final medication dose several hours prior to bedtime and the relatively short half-life of hydrocortisone). Given this uncertainty surrounding radioimmunoassay evaluation of salivary cortisol, future analyses should use liquid chromatography tandem mass spectrometry. Given the unusual finding that cortisol concentrations increased from bedtime to midnight in both patients and controls, further studies are needed to confirm the associations we found between sleep architecture and cortisol levels.

Furthermore, the fact that we gathered sleep data in a laboratory setting, over one night, means the sleep quality/architecture we analyzed may not accurately reflect participants' normal home-based sleep patterns (Lipinska & Thomas, 2017). Although our analyses comparing subjective to objective sleep measures suggested that the patterns we captured in the laboratory were similar to those participants reported experiencing at home, future research in the field might take polysomnographic measures of sleep in a more naturalistic environment and over more nights.

Regarding sample size issues, our small N meant that, for instance, we could not investigate the influence of biological sex on sleep quality/architecture in patients with AD, or the influence of certain disease characteristics on sleep and cortisol measures. It should be noted that time of last dose was relatively homogenous (6 of the 7 patients took their last dose between 14h00 and 17h00), and only two patients had any medical and psychiatric comorbidities. Therefore, any potential investigation of these variables was limited by the characteristics of the current sample.

A fruitful direction for future research might be to experimentally manipulate medication dosage and/or timing in patients with AD, and to take repeated measures with each manipulation, thus allowing each patient to act as his/her own control. This design would allow for a true

experimental test of the hypothesis that altered cortisol levels impact sleep architecture, and would help control for duration of AD diagnosis in individual patients. Similarly, future research might investigate whether modified-release hydrocortisone (which results in cortisol circadian rhythms that are more similar to those presents in healthy adults) improves sleep in patients with AD.

Summary and Conclusion

Relative to healthy controls, patients with AD who were on standard hydrocortisone replacement therapy exhibited altered cortisol diurnal rhythms, accompanied by decreases in SWS. Because SWS plays a critical role in the general physiological restorative function of sleep and in memory consolidation, disrupted sleep in patients with AD may help explain why patients often report and experience fatigue, reduced vitality, poorer health, and memory impairments. Hence, interventions focused on treating sleep disruptions in patients with AD might be especially helpful in improving specific aspects of their cognitive functioning and their overall quality of life.

CHAPTER SEVEN:

OVERALL DISCUSSION

The research described in this dissertation aimed, at its broadest neuroscientific level, to contribute to the body of literature demonstrating that disrupted sleep is a vital mechanism underlying impaired consolidation of previously learnt information. At a more specific level, the research set out to investigate relations between sleep, memory consolidation, and circadian rhythms of cortisol, in large part because separate bodies of previously published studies indicate that the sequence of, and transition between, sleep stages plays a vital role in memory consolidation, and that cortisol concentrations play a critical role in the initiation and maintenance of stages of sleep across the night.

The dissertation presented a series of four studies, each using a sample of patients with AD and matched healthy controls. Patients with AD comprised an ideal population to use in investigating the questions of interest because, despite being on lifelong GC replacement medication, they do not display a normal circadian rhythm of cortisol, and continue to experience sleep disruptions, poor memory functioning, and, overall, relatively poor quality of life.

In this chapter, I briefly summarise the findings of Studies 1-4, and elaborate on how findings from the studies are related to one another.

Summary of Study 1 - Study 4

Study 1 aimed to characterise self-reported quality of life (including, but not limited to, subjective sleep quality and cognitive impairments) in a sample of patients with AD and matched healthy controls, and to investigate whether sleep disruptions are a predictor of cognitive complaints. Findings confirmed that patients reported significantly poorer quality of life (marked by inferior sleep quality, more depressive symptomology, and a greater number of cognitive problems) than controls. Importantly, the findings from a structural

equation model demonstrated that having AD directly predicted poor quality of life and diminished sleep quality, but not cognitive problems. Instead, poor sleep in patients, and not the disease process itself, was the best predictor of cognitive impairment. Together, this set of results reinforces the notion that sleep plays a vital role cognitive functioning.

These findings from Study 1 set the stage for further investigation. In Studies 2 and 3, I used objective tests to explore whether, compared to healthy controls, patients with AD had impaired memory performance. In Studies 3 and 4, I explored whether, compared to healthy controls, patients with AD had more disrupted sleep, and whether those patterns of disruption could be a biological mechanism contributing to the observed memory impairments.

Study 2 aimed to investigate whether objective measures of cognitive performance confirmed the memory-related findings from previous studies of AD patients (including the current Study 1) that used self-report instruments. Overall, this study sought to test the hypothesis that patients with AD, in comparison to healthy controls, display impaired memory performance. Results confirmed that patients performed more poorly than controls on a test of declarative memory (they had poorer retention of previously learned information, and produced more false alarms on a recognition test), but that other domains of cognition (processing speed, attention, and executive functioning) were unimpaired. One explanation for this pattern of results is that much of declarative memory processing is centered on the hippocampus, a brain region particularly affected by alterations in cortisol concentrations. Hence, it is understandable that patients with AD, who are on lifelong GC therapy (which induces periods of sub- and supra-physiological cortisol concentrations) will display deficits on tasks assessing declarative memory.

Study 3 aimed to describe and quantify objectively measured sleep quality and memory performance in patients with AD and matched healthy controls, and to investigate whether sleep augments memory consolidation in patients as it is known to do in healthy

individuals. Results indicated that, compared to healthy controls, patients experienced poorer sleep efficiency (i.e., they spent less time asleep as a proportion of the total time spent in bed) and spent more time awake during the night. Moreover, controls retained more previously learned declarative information across the sleep-filled night, although there were no between-group retention differences on a procedural memory test. Most importantly, however, whereas controls retained significantly more declarative information when a period of sleep rather waking separated learning from recall, patients derived no such benefit. In fact, on one of the declarative memory tests, patients retained more information after a period of waking versus a period of sleep. Together, these results confirm that healthy, uninterrupted sleep is important for consolidation of previously acquired declarative information, and that patients with AD do not, because of their disrupted sleep, consolidate declarative memories as effectively as controls.

Finally, *Study 4* sought to investigate whether, in AD patients, altered cortisol rhythmicity might disrupt the normal architectural distribution of sleep (and hence, indirectly, it asked whether this mechanistic relationship could explain memory disturbances reported by, and observed in, these patients). One of the novel elements of this study was that it characterised and quantified sleep quality and architecture via polysomnographic measures. Results indicated that patients, compared to controls, had significantly less SWS and altered night-time cortisol concentrations. Specifically, patients had significantly lower cortisol concentrations 30-minutes post-awakening, and tended to have higher cortisol concentrations at both bedtime and midnight. During the first half of the night, both patients and controls experienced increasing cortisol concentrations, although the former experienced more elevated cortisol concentrations. During the second half of the night, in contrast, patient cortisol concentrations declined steeply, while control concentrations increased steadily. Furthermore, no patient mounted a cortisol awakening response, whereas 83% of controls

did. Not surprisingly, the pattern of cortisol concentrations was relatively homogenous for healthy controls, but far more variable for patients. The latter finding is most likely due to variations in medication regimen across patients, who took different doses of HC medication at different times of the day. Most interestingly, elevated cortisol concentrations were associated with less SWS across the entire sample, particularly during the first half the night, partially confirming that cortisol levels throughout the night have an important impact on sleep architecture.

Together, the findings from these four studies demonstrate that, compared to matched healthy controls, patients with AD have poorer quality of life, more disrupted sleep, deficits in verbal declarative memory, and altered night-time cortisol concentrations. Importantly, in patients, sleep-dependent memory consolidation processes are impaired, perhaps due to the altered diurnal rhythm of cortisol, and associated reduced SWS, they experience. In the next section, I delve more deeply into how the individual findings from each study come together to support those overall conclusions.

How Findings from Individual Studies Coalesce

In this section I am going to talk more about some of the individual findings (especially those that are repeated across studies) in more detail, with more attention to how they, together, fit with the existing literature.

First, it should be noted that our sample was homogenous because we used some the same participant pool across all four studies. The clinical characteristics of the patient sample were reasonably consistent across studies. In all studies, roughly 30% of the patient sample had hypothyroidism and 15% had diabetes, and, within each study sample, patients had on average 1.5 comorbid illnesses. Moreover, in each study sample (a) most patients took hydrocortisone as their glucocorticoid replacement therapy, and (b) they took, on average, 2 doses of hydrocortisone daily.

Similarly, the sociodemographic characteristics of the patient and control samples were reasonably consistent across studies. In all studies, both patients and controls had, on average, at least a matric education, controls had a normal BMI (< 25), and patients were moderately obese (BMI > 26).

Quality of life. Patients reported significantly poorer QoL, including poorer physical and mental health, less energy, more pain, poorer sleep quality, and more cognitive problems compared to matched healthy controls. This finding is consistent with a large body of evidence suggesting impaired QoL in patients with AD. Reports of depressive symptomology were significantly higher in patients than controls (*Studies 1* and *2*). This finding is consistent with previous reports of increased depression in patients with AD (Ten et al., 2001; Thomsen et al., 2006). In *Studies 3* and *4* I excluded individuals with moderate depression and therefore cannot comment about levels of depressive symptomology.

Demographic variables had little influence on quality of life. The only exception was that in both patients and controls, older age was associated with worse self-reported physical health (*Study 1*). This result is consistent with literature suggesting older age is associated with worse physical health and poorer QoL (Aaronson et al., 1998; Netuveli, Wiggins, Hildon, Montgomery, & Blane, 2006; Trief, Wade, Pine, & Weinstock, 2003). However, research has shown sexual dimorphism in QoL in patients with AD (Lovas et al., 2002; Meyer et al., 2013). For example, Lovas et al. (2002) found that mental health (as measured by the SF-36) was reduced in male patients, whereas women tend to have reduced social functioning due to emotional problems but this was limited to certain concomitant disease categories, and Meyer et al. (2013) found that overall QoL was significantly lower in females. The probable cause of this inconsistency between the current findings and those of previous studies is that, because the current sample was 75% female, adequate investigation of sex differences in QoL was not possible.

Patient disease characteristics seemed to play a minor role in quality of life. Longer disease duration was associated with worse physical health and increased daytime dysfunction, and patients who took their last dose of medication later in the day self-reported poorer QoL and more depression. These results align with a large body of research, suggesting that irrespective of replacement regimens, origin of disease or comorbidities, QoL remains impaired in adequately treated patients with AD (Alonso et al., 2004; Bleicken et al., 2008; Ekman et al., 2012; Meyer, Hackemann, Penna-Martinez, & Badenhoop, 2013). However, our results are somewhat contradictory to other previous findings in the AD literature suggesting that larger HC doses and HC/kg are associated with worse QoL (Bleicken et al., 2010; Hahner et al., 2007; Tiemensma et al., 2014). This discrepancy may be due to differences in HC regimen reported across samples. For instance, Bleicken and colleagues (2010) found that QoL was impaired in patients taking doses larger than 30mg/day (only 2 of our patients took doses larger than 30mg/day) but found no significant differences in QoL among lower doses (15-30mg). The current studies results are in concordance with the latter finding – we found no significant difference in QoL scores among our patients (5-35mg). In Tiemensma and colleagues (2014) study, patients with AD took HC doses ranging from 10-50 mg/day, whereas our samples doses ranged from 5-35mg/day. It appears that medication dosage only has a negative impact on QoL in patients taking larger doses of HC (at least 30mg/day), which could possibly explain why we found no impact of medication dosage on QoL. More studies are needed to disentangle the specific roles that adrenal failure itself, concomitant diseases, and specific disease characteristics play in determining QoL.

Cognition. Studies 1-3 share similar findings. In Study 1, patients with AD self-reported significantly more memory retrieval problems than controls. In Study 2 and Study 3, these subjective impairments were corroborated by objective measures of verbal declarative

memory – in both the latter studies, patients with AD, compared to controls, retained significantly less previously acquired information across a filled delay.

Because the hippocampus is a brain region critically involved in encoding and consolidation, and to some extent retrieval of long-term declarative memories, and because functioning of that brain region is heavily influenced by cortisol concentrations, these findings regarding impaired declarative memory in patients with AD are not surprising. Furthermore, the current findings are consistent with literature suggesting that cognitive deficits in patients with AD are limited to the domain of declarative memory.

In the current series of studies, objective data (gained via standardized paper-and-pencil and computerized tests) suggested that, relative to matched healthy controls, patients with AD displayed deficits on tasks assessing hippocampal-dependent declarative memory, but displayed intact performance on tasks assessing procedural memory (which depends more heavily on frontal, parietal, and cerebellar brain regions; Mochizuki-Kawai, 2008), and processing speed, executive functioning, and attention (all of which, from a grey matter perspective, depend more heavily on the prefrontal cortex). Previous research indicates that non-declarative forms of memory are unaffected by elevated cortisol levels (e.g., Kirschbaum et al., 1996; Lupien et al., 2007; Newcomer et al., 1994; Newcomer et al., 1999; Schwabe et al., 2009; Schwabe & Wolf, 2012), and so the fact that the current studies detected no between-group differences in performance on tasks assessing procedural memory is unsurprising. Since procedural memory relies on brain areas that do not contain a high number of MR and GR receptors (e.g., parietal and cerebellar regions), it is understandable that such a memory task is unaffected by elevated cortisol levels.

By that line of reasoning, it is surprising that performance in cognitive domains known to rely on the PFC are not impaired in patients with AD (both in the current project and in previous studies of such patients (Klement et al., 2010; Klement et al., 2009;

Schultebrasucks et al., 2015; but see Tiemensma et al., 2016). The PFC, like the hippocampus, has a high number of MR and GR receptors, and so its functioning is sensitive to the effects of altered cortisol concentrations (Arnsten, 2009; Arnsten et al., 2015). Furthermore, previous research suggests that elevated cortisol levels negatively impact performance on PFC-dependent tests of executive functioning and working memory (Cornelisse et al., 2011; De Quervain et al., 2000; McCormick et al., 2007; Wolf, Schommer, et al., 2001). In fact, there is some evidence suggesting that WM may be more sensitive than declarative memory to cortisol increases (Lupien, Gillin, et al., 1999; Wolf, Convit, et al., 2001; Young et al., 1999).

One reason why the current findings do not replicate previous data regarding altered cortisol concentrations and EF and WM performance is that here WM was only measured by the Backwards-Digit Span task and EF was only measured using a limited set of brief tests administered over the telephone. These EF and WM tasks may not have been sensitive enough to detect subtle performance deficits in performance (Egeland, 2015; Lynn & Irwing, 2008; Miyake & Friedman, 2012; Schoofs, Preuß, & Wolf, 2008; Walker & Brown, 2018). Future studies should use tasks such as the *n*-back to assess working memory, and a more comprehensive set of neuropsychological tests to assess individual domains (e.g., set-shifting, decision making, inhibition) of EF.

Associations between demographic characteristics and cognition. In Study 1, healthy older adults self-reported more problems than their younger counterparts with memory retrieval. This association was replicated with objective measures in Study 2, where, in healthy controls, older age correlated with poorer performance on the delayed recall trial of the verbal declarative memory test. Although these control-group findings are unsurprising given that they are consistent with a large literature reporting on age-related declines in memory performance (Hedden & Gabrieli, 2004; Leiva et al., 2016; Meusel et al., 2017; Park & Festini, 2017; Salthouse, 1996; Tong et al., 2013; Verhaeghen & Salthouse, 1997), they are

nevertheless of interest in the current context because this decline is attributed, at least partially, to the fact that healthy older adults experience elevated basal cortisol levels (Feller et al., 2014; Gaffey, Bergeman, Clark, & Wirth, 2016; Lupien et al., 1998; Lupien et al., 1994; Seeman et al., 1997; Wolf, Convit, et al., 2001).

The pattern of associations between age and memory performance was different in patients than in controls. In Study 1, older patients did not self-report more problems than their younger counterparts with memory retrieval, and in Study 2 analyses detected no significant association between age and delayed recall trial of the verbal declarative memory test. One way to explain this lack of association is that replacement medication may result in patients of all ages experiencing sub- and supra-physiological cortisol concentrations, and may hence lower the performance baseline for all, thereby eroding age-related differences.

Study 2 further showed that, in both patients and controls, older age was associated with slower speed of processing. This result is consistent with literature reporting on age-related declines in information processing speed (Baudouin, Clarys, Vanneste, & Isingrini, 2009; Hedden & Gabrieli, 2004; Zimprich & Martin, 2002).

It is unclear why advancing age was not associated with poorer memory performance in patients, whereas advancing age was associated with a slower processing speed. Perhaps memory systems are more sensitive to the effects of sub- and supra-physiological cortisol concentrations induced by replacement medication, and as such age-related difference are eroded.

Across the three studies that measured memory (Studies 1, 2, and 3), analyses detected no significant sex differences in cognitive performance. This result is inconsistent with a robust literature suggesting that biological sex plays an important role in mediating the relationship between cortisol concentrations and memory performance. For instance, some research indicates that older women are more susceptible than older men to the negative

effects on cognition of GCs (Seeman et al., 1997; Wolf, Kudielka, Hellhammer, Hellhammer, & Kirschbaum, 1998), but that this susceptibility is reversed in younger populations (Wolf, Convit, et al., 2001). Research has also demonstrated differences in mental ability across sexes, with men generally performing better on visuospatial tasks and mathematical reasoning, and women generally performing better on tests of verbal tests ability, fine motor skills, and perceptual speed (Hyde, 2016; Hyde, Fennema, & Lamon, 1990; Kimura, 2004; Postma, Winkel, Tuiten, & van Honk, 1999). Sex differences in cognitive abilities are due, at least in part, to the actions of sex hormones on the brain (Hampson, 1990; Kimura, 2004; Kimura & Hampson, 1994). The probable cause of this inconsistency between the current findings and those of previous studies is that, because the current sample was 75% female, adequate investigation of sex differences was not possible. Future studies of patients with AD should attempt to investigate how sex and age, both independently and interactively, impact cognitive functioning given their role in mediating relations between cortisol and memory.

Associations between disease characteristics and cognition.

Study 1, Study 2, and Study 3 were consistent in finding that, by and large, patient disease characteristics had no significant association with cognitive functioning. In Study 1, analyses detected non-significant associations between all disease characteristics and self-reported memory problems. In Study 2, analyses again detected weak and non-significant associations between disease characteristics (e.g., dose of HC medication, HC/kg ratio, number of daily doses, time of medication administration) and objectively measured cognitive performance. In Study 3, analyses also detected non-significant associations between all disease characteristics and objectively measured cognitive performance. One plausible explanation for this lack of association may be that HC administration induces sub- and supra-physiological concentrations irrespective of dose magnitude, timing, and relation to patient weight (Ross et al., 2013).

There were, however, certain disease characteristics, unrelated to dose, that proved to be associated with cognitive functioning: longer disease duration and older age at diagnosis. In Study 2, patients who had AD for longer and who were diagnosed later in life performed significantly more poorly on tests assessing information processing speed and working memory, and had overall worse cognition. In Study 2 and Study 3, longer disease duration and older age at diagnosis was significantly associated with poorer performance on tests of declarative memory.

Overall, this pattern of data is consistent with that detected in other studies of cognition in patients with AD. For example, Tiemensma and colleagues (2016) found that GC dosage and regimen did not affect memory performance, but that longer disease duration did (viz., those who had been diagnosed for a longer time performed more poorly). Other research has also found that longer duration of treatment (which, of course, is directly related to longer disease duration) is associated with poorer performance on tests of declarative and working memory (Keenan, Jacobson, Soleymani, Mayes, & Yaldoo, 1996; Tytherleigh et al., 2004). Neuroanatomical and biochemical changes due to a longer disease duration or longer periods on GC treatment may be possible explanations for these associations. For example, prolonged hypercortisolaemia may induce changes in adrenal receptors and neurotransmitters and cause structural damage to the hippocampus (De Leon et al., 1997; Lupien et al., 1998; Sapolsky et al., 1986; Segerstrom, Geiger, Boggero, Schmitt, & Sephton, 2016).

Sleep. Study 1, Study 3, and Study 4 all found that patients with AD experienced significantly more disrupted sleep than matched healthy controls. In Study 1, patients self-reported significantly poorer sleep characterised, primarily, by frequent sleep disturbances. Patients also tended to report poorer sleep quality and efficiency, and a longer sleep latency. These subjective sleep complaints were, by and large, confirmed by objective actigraphy measurements in the two later studies. In Study 3, when sleep was measured by actigraphy,

patients experienced significantly poorer sleep efficiency, attributable at least partially to significantly more awakenings after sleep onset. In contrast to the subjective reports gathered in Study 1, however, they did not objectively demonstrate longer sleep latencies. In Study 4, when sleep was measured by polysomnography, the only significant between-group difference was that patients experienced significantly less SWS than controls. In contrast to observations in Study 1 and Study 3, patients did not experience poorer sleep efficiency or more awakenings after sleep onset.

In the literature on sleep quality and architecture, dissimilarities between subjective reports and objective measures is not uncommon (Lipinska & Thomas, 2017; Løvås et al., 2003; Luyster et al., 2012). For instance, Kobayashi and colleagues (2012) found that their sample of healthy individuals and patients with PTSD underestimated total sleep time and overestimated sleep latency via self-report when compared to objective measurements.

The disparities observed here between actigraphic and polysomnographic measures is also consistent with previous findings (Paquet, Kawinska, & Carrier, 2007; Peterson et al., 2012; Sivertsen et al., 2006; but see Kushida et al., 2001; Marino et al., 2013). For example, Sivertsen and colleagues (2006) found that the actigraph underestimated total wake time, sleep latency, and overestimated total sleep time and sleep efficiency compared to PSG measurements. Actigraphy is based on the premise that there is reduced movement during sleep and increased movement during waking. However, the actigraph is prone to at least two common errors. The first involves periods of still wakefulness during sleep that are incorrectly classified as periods of sleep, and the second involves restless sleepers being incorrectly characterised as having more awakenings despite actually being asleep (Krystal & Edinger, 2008). Furthermore, although actigraphy is a reliable and valid method of assessing sleep in normal healthy individuals (Jean-Louis et al., 1996), it becomes less reliable in cases

(e.g., individuals diagnosed with insomnia) where sleep is fragmented (Paquet et al., 2007; Sivertsen et al., 2006).

Associations between demographic characteristics and sleep. Across all four studies, analyses detected hardly any associations between basic sociodemographic variables and sleep outcome variables. Without delving too deeply into the details of individual analyses, there are a couple of easily identifiable structural, or design-related, reasons for these negative findings. First, because the sample in each study included relatively few male participants, possible investigation of the association between sex and sleep, within both patient and control groups, was limited. Biological sex is an important factor to consider when studying sleep because research has shown sexual dimorphism in sleep. Men tend to have more SWS and REM, along with longer sleep and REM latencies, whereas women tend to have more N2 and WASO. Furthermore, age related declines in sleep efficiency and REM Latency, and increased N1 is more pronounced in women (Ohayon et al., 2004). The effects of ageing on HPA-axis functioning is also more pronounced in women, which could explain why sleep complaints are more common in older women compared to men (Van Cauter, Leproult, & Kupfer, 1996).

Second, investigating of the impact of age on objectively measured sleep was difficult because in *Studies 3 and 4* participants age was limited to those younger than 55 years. The strict age inclusion criteria meant we were not have been able to detect changes in sleep which are known to occur more frequently in older adults. Age is an important factor to consider when studying sleep since significant changes in sleep architecture accompany the ageing process (Martin et al., 2013; Wolkove, Elkholy, Baltzan, & Palayew, 2007). For example, total sleep time, sleep efficiency, SWS and REM are known to decline with increasing age, whereas sleep latency, WASO, N1 and N2 increase (Ohayon et al., 2004). Furthermore, some changes in sleep (i.e., decreases in SWS and REM, and increases in N1

and N2) are particularly prominent in adults over the age of 60 (Vgontzas et al., 2003). Advancing age is associated with increased evening cortisol levels and a blunted circadian rhythm of cortisol (Van Cauter et al., 1996; Vgontzas et al., 2003). These elevations in evening cortisol levels coincide with more fragmented sleep and a decline in REM in the elderly (Van Cauter et al., 2000). Given that our samples mean age in *Studies 3* and *4* was ~40 years, the current research project was not able to fully investigate the impact of age on sleep. Future studies should objectively investigate sleep across a wider age range to fully understand changes in sleep associated with ageing in patients with AD.

Associations between disease characteristics and sleep. Study 1, 3 and 4 were consistent in finding that some patient disease characteristics were significantly associated with sleep outcome variables⁹. In Study 1, patients taking larger doses of HC medication self-reported poorer overall sleep quality. This result was replicated in Study 3 and in Study 4, both of which found that larger medication doses were associated with poorer objectively-measured sleep efficiency. Moreover, in both of these latter studies, patients with higher HC/kg ratios had longer sleep latencies. These results are consistent with those reported by Smans and colleagues (2013), who found that patients with AD often experience overreplacement of cortisol in the afternoon/evening, and that sleep disturbances significantly decreased when evening overreplacement was reduced. Together, the results of that study and this one suggests that high doses of replacement medication used by patients with AD might play an important role in the sleep disturbances they experience.

Across the three studies (Studies 1, 3 and 4), no other disease characteristic was consistently associated with sleep. For example, whereas Study 1 found that longer disease duration was associated with more self-reported sleep disturbances, this association was not replicated when objective measures were used in Study 3 and in Study 4. This inconsistent

⁹ Study 2 is not included in this section since sleep was not measured in that study.

finding could be related to discrepancies between subjective reports (in Study 1) and objectively measured sleep (in Studies 3 and 4). In terms of time of last dose, one would not expect to find any consistency with regard to associations involving this variable due to disparity in range of values across studies. For instance, in Study 1 a relatively equal proportion of patients who took their last dose of medication before noon, between noon and 18h00, and after 18h00, whereas in Study 3 and in Study 4 nearly all patients took their last dose between noon and 18h00.

Limitations and Directions for Future Research

The write-up of each empirical study contained within this dissertation (i.e., Chapters 3, 4, 5, and 6) concluded with discussion of limitations of that particular study's methodological and other limitations. The current section, while acknowledging the continued existence of those individual limitations, focuses on broader limitations that cut across the research project generally. These latter limitations should be considered when evaluating the significance of the overall findings and when planning future research based on the current set of results.

First and foremost, it should be acknowledged that the QoL, memory and sleep deficits present in our patient group, which could be attributed to the inadequacy of replacement therapy to restore a normal circadian rhythm of cortisol, could also be due to several other factors. For example, the cause of AD or other coexistent endocrinopathies known to associate with AD could play a contributing role in QoL, memory and sleep. However, this was beyond the scope of the current thesis.

Despite AD being a rare clinical group, and hence generalisability to other similar medical and psychiatric conditions may be limited, we can still learn much about the interactions of HPA hormones, sleep, memory and QoL from these patients. Understanding these interactions may provide useful in studies investigating other conditions where GC

replacement medication is used (such as eczema and asthma), or conditions in which disrupted sleep is a prominent clinical feature (such as depression, PTSD, chronic fatigue syndrome, insomnia).

Comorbid medical and psychiatric conditions in patients with AD. Compared to controls, who by definition were free of any chronic illness, 41 of the 60 patients had at least one comorbid medical condition (most commonly diabetes or hypothyroidism, but also fibromyalgia, osteoporosis, and hypertension to name but a few), and 7 of the 60 patients had at least one comorbid psychiatric illness (most commonly major depressive disorder, but also PTSD, anxiety disorder and bipolar disorder), and, overall, had greater depression severity. The presence of these comorbidities should be considered when interpreting findings related to cognitive performance, and to sleep. For example, Type II diabetes and hypertension have negative effects on cognition, including domains such as processing speed, memory, executive functioning, attention and verbal fluency (Mayeda, Whitmer, & Yaffe, 2015; Taylor & MacQueen, 2007; Waldstein, 2003). Similarly, diabetes and hypothyroidism are, by themselves, associated with negative changes in sleep quality and architecture (Cappuccio et al., 2008; Parish, 2009). Major depressive disorder is characterized by a distinct pattern of abnormal sleep architecture and compromised sleep quality (Baglioni et al., 2011; Benca et al., 1992; Cole & Dendukuri, 2003; Kaplan & Harvey, 2009; Lovato & Gradsar, 2014; Murphy & Peterson, 2015; Sun et al., 2018), and individuals with high levels of depressive symptomatology experience impaired cognition in numerous domains, including memory, executive functioning, and processing speed (Burt, Zembor, & Niederehe, 1995; Donovan et al., 2017; Potter & Steffens, 2007; Rock, Roiser, Riedel, & Blackwell, 2014).

In mitigation of this potential confound, all analyses suggested that the presence of comorbid medical and psychiatric illness had little influence on cognitive performance and on sleep quality/architecture. Furthermore, because medical and psychiatric illnesses are

frequently comorbid with AD (Arlt, 2009; Meyer et al., 2013; Øksnes et al., 2012), using a sample free of such comorbidities would have been difficult to achieve, and in any case would not have been adequately representative of population of patients with AD.

Nonetheless, future studies should/might include control groups of patients who only have such comorbidities to disentangle the unique effects due to having AD versus the unique effects due to comorbid medical/psychiatric conditions.

Use of salivary cortisol samples. In Study 4, I collected salivary cortisol samples and used them as a proxy for serum cortisol levels. However, salivary cortisol is frequently undetectable, and research suggests that hydrocortisone medication may contaminate saliva (Miguel Debono et al., 2016; Lewis, 2006; Thomson et al., 2007). Therefore, the cortisol concentrations reported here may be a relatively inaccurate reflection of HPA-axis activity. Future studies should measure both salivary cortisone (which is more detectable than salivary cortisol and shows stronger relationships to serum cortisol; Debono et al., 2016) and serum cortisol, along with other hormones of the HPA-axis (e.g., ACTH, CRH, GHRH, melatonin), to fully understand hormonal influences on sleep and consequent effects on memory functioning.

Exclusive assessment of verbal declarative memory. In Study 2 and Study 3, memory functioning was assessed using data from only tests of verbal declarative memory (except in Study 3 where procedural memory was assessed). However, other forms of memory are also likely affected by alterations in cortisol concentrations and consequent sleep disruptions. For instance, emotional and spatial memory are, like verbal declarative memory, hippocampal-dependent to a large degree, and working memory relies on intact PFC processing (Arnsten, 2009; Arnsten & Pliszka, 2011; Arnsten et al., 2015; Baddeley et al., 2003; Thomas et al., 2010).

Hence, future research on relations between sleep, cortisol, and memory should add a focus on the valence of learned information that is acquired, retained, and recalled. Such investigation would be of interest because previous studies indicate that (a) positive and negative valenced material is recalled with more accuracy than neutral material (Zimmerman & Kelley, 2010), (b) increased cortisol concentrations mediate the relationship between word valence and recall performance (Kuhlmann et al., 2005; Schwabe, Bohringer, Chatterjee, & Schachinger, 2008), and (c) periods of sleep selectively enhance emotional memory (Bennion et al., 2015; Cairney, Durrant, Power, & Lewis, 2014; Groch, Wilhelm, Diekelmann, & Born, 2013; Payne et al., 2008; Wagner et al., 2001; Wagner et al., 2006; Walker & van Der Helm, 2009).

Future research should also investigate relations between sleep quality/architecture, cortisol concentrations, and spatial memory performance because previous studies have shown that (a) elevated cortisol levels (both stress-induced and exogenously administered) impair performance on spatial memory tests (Belanoff et al., 2001; Kirschbaum et al., 1996; Wolf, 2003), and (b) like performance on tests of emotional and verbal declarative memory, performance on tests of spatial memory benefits from periods of sleep (although limited research exists on the relations between sleep and spatial memory performance in humans; Peigneux et al., 2004; Stickgold, 2005).

Working memory is also negatively impacted by elevated cortisol concentrations (Lupien, Gillin, et al., 1999; Oei, Everaerd, Elzinga, van Well, & Bermond, 2006) and by sleep disruptions (Banks, 2007; Chee et al., 2006; Mu et al., 2005; Smith, McEvoy, & Gevins, 2002). Hence, future research on relations between sleep, cortisol, and memory should investigate more thoroughly their effects on working memory.

Although the series of studies presented in this thesis found that patients with AD experience deficits in verbal declarative memory, it remains unexplored as to whether all

aspects of memory processing (encoding, consolidation, and retrieval) are affected. As such, future research should disentangle which specific aspects of memory processing are impaired in patients with AD.

A potentially fruitful avenue for future studies investigating hippocampal- and/or PFC-dependent memory in patients with AD would be to consider the potential role of GR and MR occupation on test performance. Memory retrieval can be enhanced when most MRs and only some GRs are activated (i.e., when cortisol concentrations are at the top of the inverted U-shaped function). However, when circulating levels of GCs are extremely low or extremely high (i.e., when cortisol concentrations are within the tails of the inverted U-shaped function), retrieval impairments occur (De Quervain et al., 2000; Domes, Rothfischer, Reichwald, & Hautzinger, 2005; Lupien et al., 2005). Because patients with AD experience consistent periods of sub- and supra-physiological cortisol concentrations due to their replacement medication (i.e., their concentration levels may fall within the tails of the inverted U-shaped function), they may often experience memory impairments. Confirming this speculation, Tytherleigh et al. (2004) found that a balanced activation of MRs and GRs was needed for optimal performance on tests of declarative memory and working memory in adequately treated patients with AD. MRs play a particularly important role in performance on tests of hippocampal-dependent memory, executive function, and attention (Aaronson et al., 1998; Cornelisse et al., 2011; de Kloet, 2013; Hinkelmann et al., 2015; Joëls et al., 2008; Otte et al., 2015; Rimmele et al., 2013), and therefore treatment of patients with fludrocortisone may be beneficial for cognitive functioning. Further studies are needed to further investigate the impact of fludrocortisone treatment on patients cognitive functioning.

Another potentially fruitful avenue for future studies investigating hippocampal- and/or PFC-dependent memory in patients with AD would be to consider the potential role that sleep spindles play in memory consolidation processes. Sleep spindles, especially those

present during the N2 and SWS stages, appear to play a key role in sleep maintenance and sleep-dependent memory consolidation (Fogel & Smith, 2011; Genzel et al., 2009; Lüthi, 2014).

Lack of a chronic illness control group. The current design cannot confirm to what degree the findings of relatively poor QoL, disrupted sleep, and impaired cognition might be attributed to AD itself, and how much might be attributed to the mere experience of living with a chronic illness. Hence, future studies will need to include a chronic illness control group (e.g., a sample of individuals with ischemic heart disease, who like patients with AD, have a chronic illness with a life-threatening component).

Homogeneity of treatment regimens. Nearly all patients in the current series of studies were treated with immediate-release hydrocortisone. As noted above, however, new advances in treatment suggest that modified-release medication helps normalise the circadian rhythm of cortisol. The current findings therefore support speculation that employment of such regimens may have positive implications for QoL, sleep, and memory. Clearly, then, future studies should include groups of patients with AD who are on different treatment regimens (e.g., prednisone, cortisone acetate, and modified-release HC) to help determine the effects of varying treatment regimens on day- and night-time cortisol concentrations, and how, ultimately, these variations affect QoL, sleep, and memory.

Further to nearly all patients being on immediate-release hydrocortisone, nearly all patients took their last dose of medication in the late afternoon in Studies 3 and 4. As such we were unable to fully understand how timing of last dose impacts sleep and subsequent memory consolidation. Future studies might test predictions that the effects of medication on sleep and memory will depend on the time at which patients take their last dose. More specifically, adequately treated patients may experience low cortisol concentrations in the night if they take their last dose of medication earlier in the day (due to the short half-life of

HC), or high cortisol concentrations if they take their last dose of medication close to bedtime. Given the important role of cortisol in sleep timing and offset, and in the distribution of sleep stages across the night (Buckley & Schatzberg, 2005; Dijk & Lockley, 2002; Skeldon et al., 2016; Steiger, 2002), and the vital role sleep plays in memory consolidation (Spencer et al., 2017), understanding how timing of last dose impacts night-time cortisol concentrations may help us better understand sleep-dependent memory consolidation in patients with AD.

Separation of Study 3 and Study 4. Due to logistical considerations, I was not able to combine the designs and methodologies of Study 3 and Study 4 into a single study that would have permitted firm conclusions regarding the role that sleep architecture plays in memory consolidation, and whether and how sleep outcome variables and night-time cortisol concentrations interact to influence the process of sleep-dependent memory consolidation. Future studies should consider using a portable PSG device that will allow measurement of sleep in the home environment (as this may encourage more participants to take part in research projects such as this one), and will simultaneously allow firmer conclusions to be made about the role that sleep architecture plays in memory consolidation (since measurement of sleep in the home environment could provide a more realistic representation of participants natural/typical sleep). In future studies, actigraphy should be used as a complementary assessment to PSG, along with subjective questionnaires to fully understand sleep patterns in patients with AD.

CHAPTER EIGHT:

SUMMARY AND CONCLUSION

The research described in this doctoral dissertation set out to demonstrate that disrupted sleep has a significant impact on night-time memory consolidation, and that the hormone cortisol may play an important role in mediating this relationship. I used patients with AD to explore these research questions because they experience periods of sub- and supra-physiological cortisol concentrations (due to lifelong GC replacement medication), and report experiencing disrupted sleep and poor memory. As such, patients with AD provide a unique opportunity to simultaneously study the effects of hyper- and hypo-cortisolism on sleep quality, memory performance, and sleep-dependent memory consolidation.

The novelty of the research program described in this dissertation is that it investigates the relationship between altered nocturnal circadian rhythms, sleep architecture, and cognitive functioning in patients with AD. Prior to the current investigations, no published study had undertaken to investigate, in patients with AD, (a) associations between sleep disruptions and memory impairments, (b) the various types of memory systems and processes that might be affected, or (c) how these memory deficits relate to altered circadian rhythms and consequent sleep disruptions.

Cognitive results indicated that patients with AD, relative to matched healthy controls, performed poorly on tests of verbal declarative memory, but demonstrated intact performance on tests of procedural memory, processing speed, attention, and executive functioning. More importantly in terms of the research questions under consideration, patients did not derive the same memory consolidation benefit from sleep as controls did. In fact, patients performed more poorly when a period of sleep rather than waking separated learning from recall. Together, these results allow the suggestion that neurobiological

processes unique to sleep, as a special state of consciousness, play a vital role in memory consolidation.

Sleep results indicated that patients with AD reported experiencing poorer sleep quality, and demonstrated objectively poorer sleep quality, compared to matched healthy controls. Sleep architectural disturbances were, however, limited to a reduction in SWS. Although this research project's design does not permit direct inferences about relations between reduced SWS and poor memory performance, such an association would be defensible given that many previous studies confirm that SWS plays a key role in memory consolidation.

Cortisol results suggested that, in both patients and controls, elevated night-time concentrations of the hormone were associated with reductions in SWS. This result permits that tentative suggestion that cortisol plays an important role in sleep architecture.

In closing, further research is needed to fully understand the link between sleep, memory, and cortisol in general, and in patients with AD specifically. In the latter case, changes in sleep and memory associated with adrenal insufficiency could be due to alterations in hormonal functioning that arise due to replacement medication regimens. Future studies measuring the acute short-term and chronic long-term effects of GCs will be beneficial in unravelling their exact impact on human cognition and sleep.

Finally, several previous studies have shown that poor QoL may be due to GC overreplacement in patients with AD. On the other hand, the quality of an individual's cognitive functioning, their sleep, and their mood all contribute to overall QoL. Hence, memory deficits, sleep disruptions, and increased rates of depression in patients with AD may partially explain why, despite being on replacement therapy, QoL remains severely impaired in these patients. In addition, memory deficits may also be due to GC overreplacement in patients with AD. On the other hand, the quality of an individual's sleep contributes to

memory consolidation and is influenced by cortisol concentrations. As such, periods of sub- and supra-physiological cortisol concentrations induced by replacement medication may partially explain why sleep is disrupted and consequently, why memory is impaired in these patients. Given these twin assaults on the QoL and memory of patients with AD, behavioural treatments focused on improving sleep, as well as pharmacological treatments designed to minimize the side effects of conventional replacement medication, may be useful additions that will help improve the QoL and cognitive functioning of patients with AD. Overall then, this research project bolsters the scientific view that sleep is a vital biological process linked to physical, psychological and cognitive well-being.

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Appendix A

Addison's Disease Group's Socio-demographic Questionnaire

1. Date of birth (date/month/year): _____
2. Age: _____
3. What is your home language? (circle only one option)
English Afrikaans Xhosa Zulu Pedi

Other (please specify) _____
4. Sex (circle one): Male Female
5. Race (circle one): Black White Coloured Asian

Other (specify) _____
6. Height (metres): _____
7. Weight (kilograms): _____
8. Marital status (circle one): Married Single Divorced
9. Highest degree or grade completed: _____
10. Occupation (circle one):
 - a) Unemployed
 - b) Self-employed
 - c) Business employed
 - d) Student/pupil
 - e) Other (please specify) _____

11. What is the total monthly income of the household in which you live? If you are a student please take care to put your immediate caregiver's monthly income not your own. (please circle only one option):

R0 – R499

R500 – R999

R1000 – R2499

R2500 – R5499

R5500 – R9999

R10000 – R20000

R20000 – R30000

R30000 +

12. How would you describe your dwelling?

- a) Shack
- b) Wendy house or backyard dwelling
- c) Flat/ apartment
- d) Town house/ semidetached house
- e) Freestanding house
- f) Other (specify):

13. Which of these items do you have in your home? (circle as many as necessary)

Tap water

Flush toilet inside home

Electricity

Car

Telephone (landline)

Television

Computer

14. How many people sleep in the same room with you at night when you are at home?

(circle one)

- a) One
- b) Two
- c) Three
- d) Four
- e) Five
- f) More than five
- g) None

15. a) Do you smoke?

Yes

No

b) If so how many/day:

16. a) Do you drink alcohol? Yes No
b) If so how many units per week (one unit equals one glass on wine): _____

17. When were you first diagnosed with Addison's Disease? _____

18. When did you start taking your medication for Addison's Disease? _____

19. What medications are you on for Addison's Disease?

20. What is your daily dosage? _____

21. At what times of day do you take your medication? _____

22. Do you have any other illnesses (both physical and mental) that have been diagnosed by a qualified doctor?

Appendix B
Healthy Control Group's Socio-demographic Questionnaire

1. Date of birth (date/month/year): _____
2. Age: _____
3. What is your home language? (circle only one option)
English Afrikaans Xhosa Zulu Pedi

Other (please specify) _____
4. Sex (circle one): Male Female
5. Race (circle one): Black White Coloured Asian

Other (specify) _____
6. Height (metres): _____
7. Weight (kilograms): _____
8. Marital status (circle one): Married Single Divorced
9. Highest degree or grade completed: _____
10. Occupation (circle one):
 - f) Unemployed
 - g) Self-employed
 - h) Business employed
 - i) Student/pupil
 - j) Other (please specify) _____

11. What is the total monthly income of the household in which you live? If you are a student please take care to put your immediate caregiver's monthly income not your own. (please circle only one option):

R0 – R499

R500 – R999

R1000 – R2499

R2500 – R5499

R5500 – R9999

R10000 – R20000

R20000 – R30000

R30000 +

12. How would you describe your dwelling?

g) Shack

h) Wendy house or backyard dwelling

i) Flat/ apartment

j) Town house/ semidetached house

k) Freestanding house

l) Other (specify):

13. Which of these items do you have in your home? (circle as many as necessary)

Tap water

Flush toilet inside home

Electricity

Car

Telephone (landline)

Television

Computer

14. How many people sleep in the same room with you at night when you are at home?

(circle one)

h) One

i) Two

j) Three

k) Four

l) Five

m) More than five

n) None

15. a) Do you smoke?

Yes

No

b) If so how many/day: _____

16. a) Do you drink alcohol? Yes No

b) If so how many units per week (one unit equals one glass of wine): _____

17. Do you have any other illnesses (both physical and mental) that have been diagnosed by a qualified doctor?

18. Do you take any form of medication? (if yes please specify)

Appendix C

Consent Form for Study 1

Informed Consent to Participate in Research and Authorization for Collection, Use, and Disclosure of Protected Health Information

This form provides you with information about the study and seeks your authorization for the collection, use and disclosure of your information necessary for the study. The Principal Investigator (the person in charge of this research) or a representative of the Principal Investigator will also describe this study to you and answer all of your questions. Your participation is entirely voluntary. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. By participating in this study you will not be penalized or lose any benefits to which you would otherwise be entitled.

1. Name of Participant ("Study Subject")

2. Title of Research Study

Quality of life, cortisol and sleep architecture: An associative role in cognitive functioning in patients with Addison's disease.

3. Principal Investigators, Ethics Committee, and Telephone Number(s)

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4. What is the purpose of this research study?

This research aims to investigate the quality of life of patients with Addison's Disease in a South African context. The results from the analysis of these questionnaires will guide further studies in the principal investigator's doctoral degree.

5. What will be done if you take part in this research study?

This study requires you to fill out a number of questionnaires in your own time. The questionnaires relate to demographic information, quality of life, sleeping habits, mood, and cognition.

6. If you choose to participate in this study, how long will you be expected to participate in the research?

You may fill out the questionnaires at your convenience, and there is no time limit in which to do so.

7. How many people are expected to participate in the research?

400

8. What are the possible discomforts and risks?

There are no discomforts and risks associated with participation in this study.

9. What are the possible benefits of this study?

Participation in this study will improve our understanding of what factors affect the quality of life in patients with Addison's disease in a South African context. This knowledge may be useful for future studies aimed at further understanding how low cortisol levels impact cognition, and may be applied to treatment for chronic corticosteroid deficiencies such as Addison's disease.

10. If you choose to take part in this research study, will it cost you anything?

Participating in this study will not cost you anything.

11. Can you withdraw from this research study and if you withdraw, can information about you still be used?

You are free to withdraw your consent and to stop participating in this research study at any time. If you do withdraw your consent, there will be no penalty. Information already collected may be used.

If you have any questions regarding your rights as a research subject, you may phone the Psychology Department offices at 021-650-3430.

12. Once personal and performance information is collected, how will it be kept secret (confidential) in order to protect your privacy?

Information collected will be stored in locked filing cabinets or in computers with security passwords. Only certain people have the right to review these research records. These people include the researchers for this study and certain University of Cape Town officials. Your research records will not be released without your permission unless required by law or a court order.

13. What information about you may be collected, used and shared with others?

If you agree to be in this research study, it is possible that some of the information collected might be copied into a “limited data set” to be used for other research purposes. If so, the limited data set may only include information that does not directly identify you. For example, the limited data set **cannot** include your name, address, telephone number, ID number, or any other photographs, numbers, codes, or so forth that link you to the information in the limited data set.

14. How will the researcher(s) benefit from your being in the study?

Information from this study will be utilised to better understand how quality of life psychological well-being are impacted by Addison’s disease and by living in a South African context. This may have important implications in the treatment of patients with cortisol deficiencies such as those seen in patients with Addison’s disease, and what we can do to improve their quality of life and psychological well-being.

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator and others attached to this research project may benefit if the results of this study are presented at scientific meetings or in scientific journals. This study is being undertaken for the Principal Investigator’s doctorate degree.

15. Signatures

As a representative of this study, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; and how the participant’s performance and other data will be collected, used, and shared with others:

Signature of Person Obtaining Consent and Authorization Date

You have been informed about this study’s purpose, procedures, possible benefits, and risks; and how your performance and other data will be collected, used and shared with others. You have received a copy of this form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time.

You voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your performance and other data. By signing this form, you are not waiving any of your legal rights.

Signature of Person Consenting and Authorizing

Date

Please indicate below if you would like to be notified of future research projects conducted by our research group:

_____ (initial) Yes, I would like to be added to your research participation pool and be notified of research projects in which I might participate in the future.

Method of contact:

Phone number: _____

E-mail address: _____

Mailing address: _____

Appendix D

Advertisement for Study 1



Department of Psychology
University of Cape Town Rondebosch 7701 South Africa
Telephone (021) 650 9111
Fax No. (021) 650 4104

ARE YOU BETWEEN THE AGES OF 20 AND 80 YEARS?

The Department of Psychology at the University of Cape Town is currently running a study on Quality of Life in a South African Context, and is looking for members of the general population to take part.

What do I have to do if I decide to take part?

You will be required to fill out a number of questionnaires relating to quality of life, sleep, stress, cognition, coping style, and emotion. This is the only thing you will have to do for the study.

How do I know if I qualify to take part?

If you are between the ages of 20 and 80 and have no form of chronic illness, you qualify to take part.

What are the benefits and risks of taking part? This information will be used for a larger study in the researcher's doctorate degree. The aim of the larger study is to improve our understanding of what factors affect the quality of life and psychological well-being in patients with Addison's disease in a South African context. This knowledge may be useful for future studies aimed at further understanding how low cortisol levels impact cognition and quality of life, and may be applied to treatment for chronic corticosteroid deficiencies such as Addison's disease.

There are no discomforts and risks associated with participation in this study, and participation in this study will cost you nothing.

I'm interested in taking part, who do I contact?

You can contact the principal researcher, Michelle Henry via email at mhmish@gmail.com, or via telephone at 021 – 551 6534. You may also contact the researcher if you have any questions you want to ask before deciding to take part in the study.

Appendix E

Scoring the BTACT using Bi-factor Method

Methods

Data Management and Statistical Analyses

Scoring the BTACT and deriving outcome variables. In addition, we scored the BTACT and derived a set of z-scores using the bi-factor scoring method outline by Gavett and colleagues (2013). In this method of scoring, linear regression based models are used to predict bi-factor BTACT z-scores, that account for age, education, gender, and occupation-alone, and in various combinations.

Results

Table A presents between-group comparisons (i.e., independent samples *t*-tests) of Bi-factor scored BTACT outcome variables. Patients with AD performed significantly more poorly than healthy controls on all outcomes.

Table A
Comparison of Group Performance on the Bi-factor scored BTACT (Z-scores) (N = 67)

Variable	AD ^a	Healthy Controls ^c	<i>t</i>	<i>p</i>	ESE
	(<i>n</i> = 33)	(<i>n</i> = 34)			
Unadjusted	-0.26 (1.05)	0.16 (0.88)	1.80	.038*	0.43
Adjusted for age	-0.71 (1.13)	-0.01 (1.04)	2.64	.005*	0.65
Adjusted for age, gender	-0.73 (1.12)	0.01 (1.03)	2.83	.003*	0.69
Adjusted for age, education	-0.63 (1.13) ^b	0.07 (1.00)	2.69	.005*	0.66
Adjusted for age, gender, education	-0.67 (1.11) ^b	0.03 (1.00)	2.72	.005*	0.66

Note. Means are presented with standard deviations in parentheses. BTACT = Brief Test of Adult Cognition by Telephone; AD = Addison's disease; ESE = effect size estimate (in this case, Cohen's *d*).

^aData based on 33 patients in the AD group (z-scores from these participants in each group could not be calculated due to incomplete Red-Green total score data).

^bData based on 32 participants (1 patient did not provide information on their education)

^c Data based on 34 participants in the control group (z-scores from these participants in each group could not be calculated due to incomplete Red-Green total score data).

* $p < .05$.

Associations Between Demographic and Cognitive Variables

Within each group, we calculated associations between demographic (age, education, gender, income, and BDI-II (depression)) variables and each of the BTACT outcome variables. For the continuous variables age, education, and BDI-II, we performed Pearson's r correlations, and for the categorical variable gender we performed Fischer's Exact tests (because >20% of cell counts were less than 5)

Within the AD group, the analyses detected a negative association between age and Unadjusted z-score ($r = -.39, p = .012$). The analyses detected positive associations between education and (a) Unadjusted z-score ($r = .52, p = .002$), (b) z-score adjusted for age ($r = .41, p = .011$), and (c) z-score adjusted for age and gender ($r = .42, p = .009$).

Within the control group, the analyses detected a negative association between age and Unadjusted z-score ($r = -.39, p = .011$). The analyses detected positive associations between education and (a) z-score adjusted for age ($r = .39, p = .011$), and (b) z-score adjusted for age and gender ($r = .39, p = .012$).

A series of Fisher's Exact Tests sought to determine whether, each group, there was an association between gender and BTACT outcome variable scores. The analyses detected no significant associations, all $ps > .073$, Cramer's $Vs < 1.00$.

Associations Between Disease Characteristics and Cognitive Variables

Table B presents the results of correlational analyses investigating associations between disease characteristics and cognitive performance in the AD group only. None of the disease characteristics correlated significantly with any bi-factor z-scores.

Table B

Correlation of Bi-Factor z-scores with Addison's Disease Clinical Characteristics

	Age at diagnosis	Time since diagnosis	Total HC dose ^a	HC/kg ^a	Number of doses/day
Bi-factor Z-scores ^b					
Unadjusted	-0.25	-0.16	< -0.01	0.09	0.13
Adjusted for age	-0.07	0.06	-0.12	0.05	0.11
Adjusted for age, gender	-0.08	0.07	-0.12	0.04	0.11
Adjusted for age, education ^c	0.04	0.01	-0.09	0.07	0.08
Adjusted for age, gender, education ^c	0.03	0.01	-0.07	0.06	0.08

Note. Statistic presented is Pearson's r correlation coefficient. p -values are presented in parentheses for statistically significant correlations. HC = hydrocortisone.

^aData based on 32 participants (1 patient did not provide information on their hydrocortisone dosage, and 4 were prescribed prednisone).

^bData based on 33 participants (z-scores from 2 patients could not be calculated due to incomplete Red-Green data).

^cData based on 32 participants (1 patient did not provide information on their education).

* $p < .05$.

A series of Fisher's Exact Tests sought to determine whether, in the AD group, there was an association between timing of the last dose (before noon, $n = 8$; between noon and 18h00, $n = 11$; after 18h00, $n = 16$) and Bi-factor z-scores. The analyses detected no significant associations.

We ran a set of secondary analyses to determine whether the character of certain comorbid illnesses in the AD patient group influenced their cognitive functioning. Since the most common comorbid illnesses were hypothyroidism (22.9%, 8 people) and diabetes mellitus (22.9%, 8 people), two separate independent samples t -test compared BTACT performance in patients who had diabetes mellitus versus those who did not, and in patients who had hypothyroidism versus those who did not. There were no significant between-group differences on any of the outcome variables in the diabetes analysis ($ps > .06$). However, when comparing patients who had hypothyroidism versus those who did not, the following statistically significant between-group differences arose: (a) z-score adjusted for age and education (patients with hypothyroidism: $M = 0.06$, $SD = 0.99$; patients without

hypothyroidism: $M = -0.87$, $SD = 1.10$; between-group comparison, $t(30) = -2.12$, $p = .043$), and (b) z-score adjusted for age, education, and gender (patients with hypothyroidism: $M = -0.01$, $SD = 0.96$; patients without hypothyroidism: $M = -0.90$, $SD = 1.09$; between-group comparison, $t(30) = -2.06$, $p = .048$).

Appendix F
Advertisement for Study 3

INTERESTED IN TAKING PART IN A SLEEP STUDY?

The Department of Psychology at the University of Cape Town is currently running a study on the effects of cortisol levels on sleep and cognition.

What do I have to do if I decide to take part?

In this experiment, you will be required to perform a morning and evening of memory testing (typically lasting one hour each), then to wear an actigraph for 1 week and keep a sleep diary each day, and then perform another morning and evening of memory testing (typically lasting one hour each) one week later.

The study will be arranged at least one week in advance, at a time convenient to you. You will retain your routine bedtime and waking time.

After this final session of memory testing you will be informed in detail about the design of the study and the research questions we hope to address with this study. You will also have the opportunity to ask questions and thus learn more about psychological research.

How do I know if I qualify to take part?

If you are between the ages of 18 and 55 years, are not on any oral contraceptives, have not been through menopause, are not pregnant you qualify to take part in this study.

What are the benefits and risks of taking part?

In exchange for participation, you will be **paid R500**.

You will also get the opportunity to ask the researcher any questions you might have about sleep and cognition. There are no immediately identifiable serious risks from you participating. All possible risks will be explained to you when you meet with the researcher.

I'm interested in taking part, what do I do?

Please tick the YES box if you are interested in taking part in this study, and the NO box if you are not.

YES ☐

NO ☐

You can contact the principal researcher, Michelle Henry via email at mhmish@gmail.com, or via telephone at 021 – 551 6534 if you have any questions you want to ask before deciding to take part in the study.

Appendix G

Consent Form for Study 3

Informed Consent to Participate in Research and Authorization for Collection, Use, and Disclosure of Protected Health Information

This form provides you with information about the study and seeks your authorization for the collection, use and disclosure of your sleep architecture patterns and cognitive performance data, as well as other information necessary for the study. The Principal Investigator (the person in charge of this research) or a representative of the Principal Investigator will also describe this study to you and answer all of your questions. Your participation is entirely voluntary. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. By participating in this study you will not be penalized or lose any benefits to which you would otherwise be entitled.

16. Name of Participant ("Study Subject")

17. Title of Research Study

Quality of life, cortisol and sleep architecture: An associative role in cognitive functioning.

18. Principal Investigator and Telephone Number(s)

Kevin G. F. Thomas, Ph.D.
Department of Psychology
University of Cape Town
021-650-4608

Michelle Henry, MA
PhD Candidate
Department of Psychology
University of Cape Town
021-551-6534

Faculty of Health Sciences
Research Ethics Committee
Room E52-24, Groote Schuur Hospital, Old Main Building
Observatory 7925
Tel: 021-406-6338
Fax: 021-406-6411
Email: lames.emjedi@uct.ac.za

19. What is the purpose of this research study?

This research aims to investigate the effects of cortisol levels on i) memory and attention, and ii) sleep patterns

20. What will be done if you take part in this research study?

In this experiment, you will be required to perform a morning and evening of memory testing, then to wear an actigraph for 1 week and keep a sleep diary each day, and then perform another morning and evening of memory testing.

The study will be arranged at least one week in advance, at a time convenient to you. You will retain your routine bedtime and waking time. On the first day the researcher will come to your house in the morning at 07 00 (Group 1) or in the evening at 18 30 (Group 2) and you will be briefed once more, in detail, on the procedure. Before commencing the actual study, you will undergo a screening process whereby the Principal Investigator listed in # 3 of this form will administer a short psychiatric questionnaire, an IQ, and other questionnaires regarding mood and sleep to you. These tools are not meant to categorise you in any way and won't be used for any diagnostic purpose. They are merely research instruments that allow us to identify certain patterns of interest.

You will be attached to actigraph which is a small device worn on an elastic belt around your hip that measures body movement. You will continue wearing this device for the following 1 week. The researcher will explain how you complete the sleep diary, which you will be required to fill out each day for the following week. You will then be required to do a short series of memory and attention tasks, typically lasting 1 hour. The researcher will then leave, and return the following morning at 07 00 (Group 2) or that evening at 19 00 (Group 1) for you to do a short series of memory and attention tasks (lasting about 1 hour).

One week after the initial day the researcher will return to your house at 07 30 (Group 2) or 19 00 (Group 1) and you will again be required to do a short series of memory and attention tasks, typically lasting 1 hour. The researcher will leave and return at 19 00 (Group 2) or the following morning 07 00 (Group 1), when you will again be required to do a short series of memory and attention tasks, typically lasting 1 hour. The actigraph will be removed after the memory testing session is over.

After this final session of memory testing you will be informed in detail about the design of the study and the research questions we hope to address with this study. You will also have the opportunity to ask questions and thus learn more about psychological research. If you have any questions now or at any time during the study, you may contact the Principal Investigator listed in #3 of this form.

This study has been approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town and you should feel free to contact Professor Marc Blockman, chairperson of the committee (021 4066496), if you have any concerns about your rights and welfare as a research participant.

21. If you choose to participate in this study, how long will you be expected to participate in the research?

The sleep study will take place over a 1 week period, requiring you to wear an actigraph for 1 week and keep a sleep diary each day. You will also be required to complete two mornings and evenings of memory testing.

22. How many people are expected to participate in the research?

23. What are the possible discomforts and risks?

The actigraph is a small device (about the size of a matchbox) worn around your hip on an elastic belt. It should cause no discomfort or inconvenience to wear it over a 1 week period.

10a. What are the possible benefits to you?

You may or may not personally benefit from participating in this study. Participation in this study may, however, improve your understanding of some factors that affect sleep and cognitive functioning.

10b. What are the possible benefits to others?

The information from this study may help improve our understanding of certain mechanisms underlying the process of memory functioning and the impact of certain hormones on sleep and memory. This research will provide us with a better understanding of the widespread effects of cortisol on cognition.

11. If you choose to take part in this research study, will it cost you anything?

Participating in this study will not cost you anything.

12. Will you receive compensation for taking part in this research study?

You will receive financial compensation of the amount of R500 for your participation in the study.

13a. Can you withdraw from this research study?

You are free to withdraw your consent and to stop participating in this research study at any time. If you do withdraw your consent, there will be no penalty.

If you have any questions regarding your rights as a research subject, you may phone the Psychology Department offices at 021-650-3430.

13b. If you withdraw, can information about you still be used and/or collected?

Information already collected may be used.

14. Once personal and performance information is collected, how will it be kept secret (confidential) in order to protect your privacy?

Information collected will be stored in locked filing cabinets or in computers with security passwords. Only certain people have the right to review these research records. These people include the researchers for this study and certain University of Cape Town officials. Your research records will not be released without your permission unless required by law or a court order.

15. What information about you may be collected, used and shared with others?

This information gathered from you will be demographic information, movement (from the Actigraph), performance on cognitive tests, and scores on the IQ test, psychiatric inventory, depression and anxiety inventory, and subjective sleep measures (the sleep diary). If you agree to be in this research study, it is possible that some of the information collected might be copied into a “limited data set” to be used for other research purposes. If so, the limited data set may only include information that does not directly identify you. For example, the limited data set **cannot** include your name, address, telephone number, ID number, or any other photographs, numbers, codes, or so forth that link you to the information in the limited data set.

16. How will the researcher(s) benefit from your being in the study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator and others attached to this research project may benefit if the results of this study are presented at scientific meetings or in scientific journals. This study is being undertaken for the Principal Investigator’s doctorate degree.

17. Signatures

As a representative of this study, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; and how the participant’s performance and other data will be collected, used, and shared with others:

Signature of Person Obtaining Consent and Authorization Date

You have been informed about this study’s purpose, procedures, possible benefits, and risks; and how your performance and other data will be collected, used and shared with others. You have received a copy of this form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time.

You voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your performance and other data. By signing this form, you are not waiving any of your legal rights.

Signature of Person Consenting and Authorizing Date

Please indicate below if you would like to be notified of future research projects conducted by our research group:

_____ (initial) Yes, I would like to be added to your research participation pool and be notified of research projects in which I might participate in the future.

Method of contact:

Phone number: _____

E-mail address: _____

Mailing address: _____

Appendix H

Study 3 Results using Independent Sample *t*-tests

Note: In our original manuscript we used independent sample *t*-tests to analyse the following data. However, a specific reviewer requested we use dependent sample *t*-tests. Therefore, I am reporting both sets of results. The pattern of results remains the same irrespective of the type of *t*-test performed.

Sample Characteristics

Table C presents the demographic characteristics of our sample, as well as their BDI-II and Shipley IQ data.

Table C
Sample Demographic Characteristics (N = 20)

Characteristic	Group		Test statistic	<i>p</i>	ESE
	AD (<i>n</i> = 10)	Healthy (<i>n</i> = 10)			
Age (years)	42.00 (10.07)	40.30 (11.62)	<i>t</i> (18) = 0.35	.731	0.16
Education (years)	13.80 (2.44)	13.50 (1.58)	<i>t</i> (18) = 0.33	.748	0.15
BMI ^a	28.94 (5.29) ^b	23.40 (2.31)	<i>U</i> = 11.00	.042*	1.51
Income			$\chi^2(4) = 4.40$.384	.355
2500 – 5499	10 (1)	0 (0)			
5500 – 9999	10 (1)	0 (0)			
10000 – 19999	30 (3)	10 (1)			
20000 – 30000	10 (1)	30 (3)			
30000+	40 (4)	60 (6)			
BDI-II					
Time 1	9.90 (7.91)	7.70 (5.76)	<i>t</i> (18) = 0.71	.486	0.32
Time 2	7.89 (7.61) ^c	7.22 (8.14) ^d	<i>t</i> (16) = 0.18	.860	0.09
Shipley IQ	94.50 (15.31)	105.70 (11.35)	<i>t</i> (18) = -1.86	.080	0.83

Note. For all variables except Income, means are provided with standard deviations in parentheses. For Income, data provided are % of sample with *n* in parentheses.

BMI = body mass index. BDI-II = Beck Depression Inventory – Second Edition. ESE = effect size estimate; in this case, Cohen's *d* for *t*-tests and Cramer's *V* for chi-square.

^aMann-Whitney *U* Test performed. In this case test statistic = *U*, effect size = *r*.

^bData based on 6 participants (4 patients did not provide information on their height).

^cData based on 9 participants (1 patient did not complete this measure at Time 2).

^dData based on 9 participants (1 participant did not complete this measure at Time 2).

**p* < .05.

By design, there were no significant between-group differences in terms of age ($p = .731$), income ($p = .384$), education ($p = .748$), sex distribution, and race distribution. The analysis also detected no significant between-group differences in terms of IQ ($p = .080$). It did, however, detect significant between-group differences in terms of BMI ($p = .042$).

Regarding BDI-II scores, analyses detected no significant between-group differences, at either the first ($p = .486$) or second ($p = .860$) measurement point. Of note here is that (a) across the sample, scores were relatively stable from one measurement point to the next (test-retest reliability = .87), and (b) within each group, the average BDI-II score fell in the range conventionally described as “minimally depressed” (0-13 points; Beck et al., 1996).

Between-group Comparisons: Sleep Data

Table D presents descriptive data for participants’ activity during the *Sleep* condition, as well as the results of statistical analyses testing the prediction that, for all sleep variables, healthy controls would experience more favourable outcomes.

Table D
Participants’ Activity during the Sleep Condition (N = 16)

Outcome variable	AD	Healthy	<i>t</i>	<i>p</i>	ESE
	(<i>n</i> = 8) ^a	(<i>n</i> = 8) ^b			
Total Sleep Time (mins.)	440.00 (72.42)	396.25 (52.09)	1.39	.094	0.69
Sleep Latency (mins.)	9.38 (15.37)	1.88 (3.72)	1.34	.109	0.67
WASO (mins.) ^c	28.38 (28.11)	7.63 (12.74)	9.00	.008*	0.95
Sleep Efficiency (%)	91.78 (4.26)	97.18 (2.69)	-3.03	.005*	1.52
Number of Awakenings ^c	3.00 (2.61)	0.75 (0.89)	14.00	.033*	1.15

Note. Means are presented, with standard deviations in parentheses. All *p*-values presented are one tailed. AD = Addison’s disease; WASO = wake after sleep onset; ESE = effect size estimate; in this case, Cohen’s *d*.

^aOf the initial sample of 10 patients with AD, two did not complete the diary and did not wear the actigraph on the Sleep Condition night.

^bOf the initial sample of 10 healthy controls, two did not wear the actigraph on the Sleep Condition night.

^cMann-Whitney *U* Test performed. In this case test statistic = *U*, effect size = *r*.

* $p < .05$.

As the table shows, the analyses detected significant-between-group differences with regard to WASO ($p = .008$), Sleep Efficiency ($p = .005$) and Number of Awakenings ($p = .033$). After the Bonferroni correction, only two between-group differences remained significant: WASO and Sleep Efficiency. The descriptive statistics suggest that, on average, healthy controls achieved a full night of relatively uninterrupted sleep, whereas patients experienced interrupted sleep characterised by poorer sleep efficiency and more time spent awake.

Appendix I
Consent Form for Study 4

***Informed Consent to Participate in Research
and Authorization for Collection, Use, and
Disclosure of Protected Health Information***

This form provides you with information about the study and seeks your authorization for the collection, use and disclosure of your sleep architecture patterns and cognitive performance data, as well as other information necessary for the study. The Principal Investigator (the person in charge of this research) or a representative of the Principal Investigator will also describe this study to you and answer all of your questions. Your participation is entirely voluntary. Before you decide whether or not to take part, read the information below and ask questions about anything you do not understand. By participating in this study you will not be penalized or lose any benefits to which you would otherwise be entitled.

24. Name of Participant ("Study Subject")

25. Title of Research Study

Quality of life, cortisol and sleep architecture: An associative role in cognitive functioning.

26. Principal Investigator and Telephone Number(s)

Kevin G. F. Thomas, Ph.D.
Department of Psychology
University of Cape Town
021-650-4608

Michelle Henry, MA
PhD Candidate
Department of Psychology
University of Cape Town
021-551-6534

Faculty of Health Sciences
Research Ethics Committee
Room E52-24, Groote Schuur Hospital, Old Main Building
Observatory 7925
Tel: 021-406-6338
Fax: 021-406-6411
Email: lames.emjedi@uct.ac.za

27. What is the purpose of this research study?

This research aims to investigate the effects of cortisol levels on i) memory and attention, and ii) sleep patterns

28. What will be done if you take part in this research study?

In this experiment, you will be called in for a sleep study on 2 nights.

The sleep study will be arranged at least one week in advance, at a time convenient to you. You will retain your routine bedtime and waking time but will be asked to avoid caffeine and sugar in your diet for a few hours before bedtime. You will be required to come to the sleep laboratory based at Vincent Pallotti Private Hospital between at 20 00 on the first night and will be briefed once more, in detail, on the procedure.

You will be hooked to a polysomnograph (PSG) which is an EEG machine designed to monitor your sleep pattern. Electrodes will be placed on your head, chest, near your chin and temples; these are completely safe and present no danger whatsoever to your health. They are designed to transmit physiological indications of the stage of sleep you are experiencing at a given point in time, to a computer monitor. One or two researchers will be surveying the monitor in an adjoining room. They will be available to you for assistance at any time. There is a panic button at your bedside should you need assistance at any point during the night. You will be woken up at 06 00 the following morning and allowed to go home after the PSG has been removed (around 07 00).

On night 2 you will be required to come to the sleep laboratory at 20 00. You will then be hooked to a polysomnograph (PSG) in the same manner as described above. A small cotton bud- shaped swab will be gently placed in your mouth, for two minutes before you go to sleep, in order to measure your natural salivary cortisol. This method is non-intrusive and will not harm or cause you discomfort in any way. The same procedure will be followed at 12 00 and when you wake up in the morning. You will be woken up at 06 00, the PSG machine will be removed, and a final salivary cortisol measure will be taken at 6 45. The experiment typically ends at 07 30 on the following morning.

After the sleep sessions are over, you will be informed in detail about the design of the study and the research questions we hope to address with this study. You will also have the opportunity to ask questions and thus learn more about psychological research. If you have any questions now or at any time during the study, you may contact the Principal Investigator listed in #3 of this form.

This study has been approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town and you should feel free to contact Professor Marc Blockman, chairperson of the committee (021 4066496), if you have any concerns about your rights and welfare as a research participant.

29. If you choose to participate in this study, how long will you be expected to participate in the research?

The sleep study will takes over 2 nights, requiring you to be in the sleep laboratory from 8pm until 7am on the first night, and from 8pm to 7:30am on the second night.

30. How many people are expected to participate in the research?

20

31. What are the possible discomforts and risks?

Sleeping in an environment other than your own bedroom might feel strange and uncomfortable at first. Great precautions will be taken to ensure your safety and comfort. The

sleep laboratory at Vincent Pallotti is fully equipped with a proper bed, clean bedding, restrooms and a kitchenette. It is situated in a secure building with adequate surveillance and alarm system. Attempts will be made to familiarise you with the PSG and the electrodes used will be padded and lubricated so as to be as non-intrusive as possible.

10a. What are the possible benefits to you?

You may or may not personally benefit from participating in this study. Participation in this study may, however, improve your understanding of some factors that affect sleep and cognitive functioning.

10b. What are the possible benefits to others?

The information from this study may help improve our understanding of certain mechanisms underlying the process of memory functioning and the impact of certain hormones on sleep and memory. This research will provide us with a better understanding of the widespread effects of cortisol on cognition.

11. If you choose to take part in this research study, will it cost you anything?

Participating in this study will not cost you anything.

13. Will you receive compensation for taking part in this research study?

You will not receive financial compensation for your participation in the study.

13a. Can you withdraw from this research study?

You are free to withdraw your consent and to stop participating in this research study at any time. If you do withdraw your consent, there will be no penalty.

If you have any questions regarding your rights as a research subject, you may phone the Psychology Department offices at 021-650-3430.

13b. If you withdraw, can information about you still be used and/or collected?

Information already collected may be used.

14. Once personal and performance information is collected, how will it be kept secret (confidential) in order to protect your privacy?

Information collected will be stored in locked filing cabinets or in computers with security passwords. Only certain people have the right to review these research records. These people include the researchers for this study and certain University of Cape Town officials. Your research records will not be released without your permission unless required by law or a court order.

18. What information about you may be collected, used and shared with others?

This information gathered from you will be records of your sleep architecture (from the PSG). If you agree to be in this research study, it is possible that some of the information collected might be copied into a “limited data set” to be used for other research purposes. If so, the limited data set may only include information that does not directly identify you. For example, the limited data set **cannot** include your name, address, telephone number, ID number, or any other photographs, numbers, codes, or so forth that link you to the information in the limited data set.

19. How will the researcher(s) benefit from your being in the study?

In general, presenting research results helps the career of a scientist. Therefore, the Principal Investigator and others attached to this research project may benefit if the results of this study are presented at scientific meetings or in scientific journals. This study is being undertaken for the Principal Investigator’s doctorate degree.

20. Signatures

As a representative of this study, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study; and how the participant’s performance and other data will be collected, used, and shared with others:

Signature of Person Obtaining Consent and Authorization Date

You have been informed about this study’s purpose, procedures, possible benefits, and risks; and how your performance and other data will be collected, used and shared with others. You have received a copy of this form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time.

You voluntarily agree to participate in this study. You hereby authorize the collection, use and sharing of your performance and other data. By signing this form, you are not waiving any of your legal rights.

Signature of Person Consenting and Authorizing Date

Please indicate below if you would like to be notified of future research projects conducted by our research group:

_____ (initial) Yes, I would like to be added to your research participation pool and be notified of research projects in which I might participate in the future.

Method of contact:

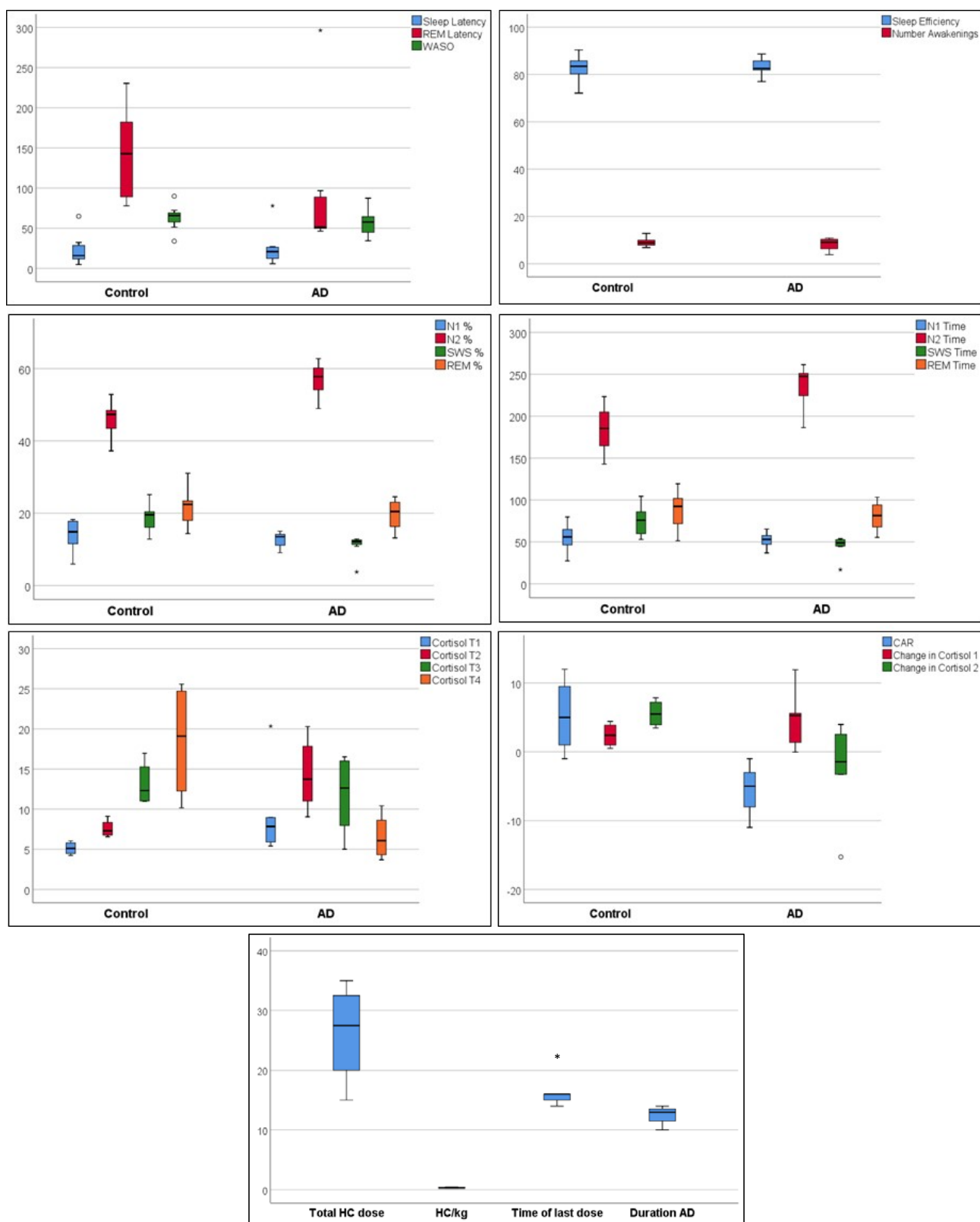
Phone number: _____

E-mail address: _____

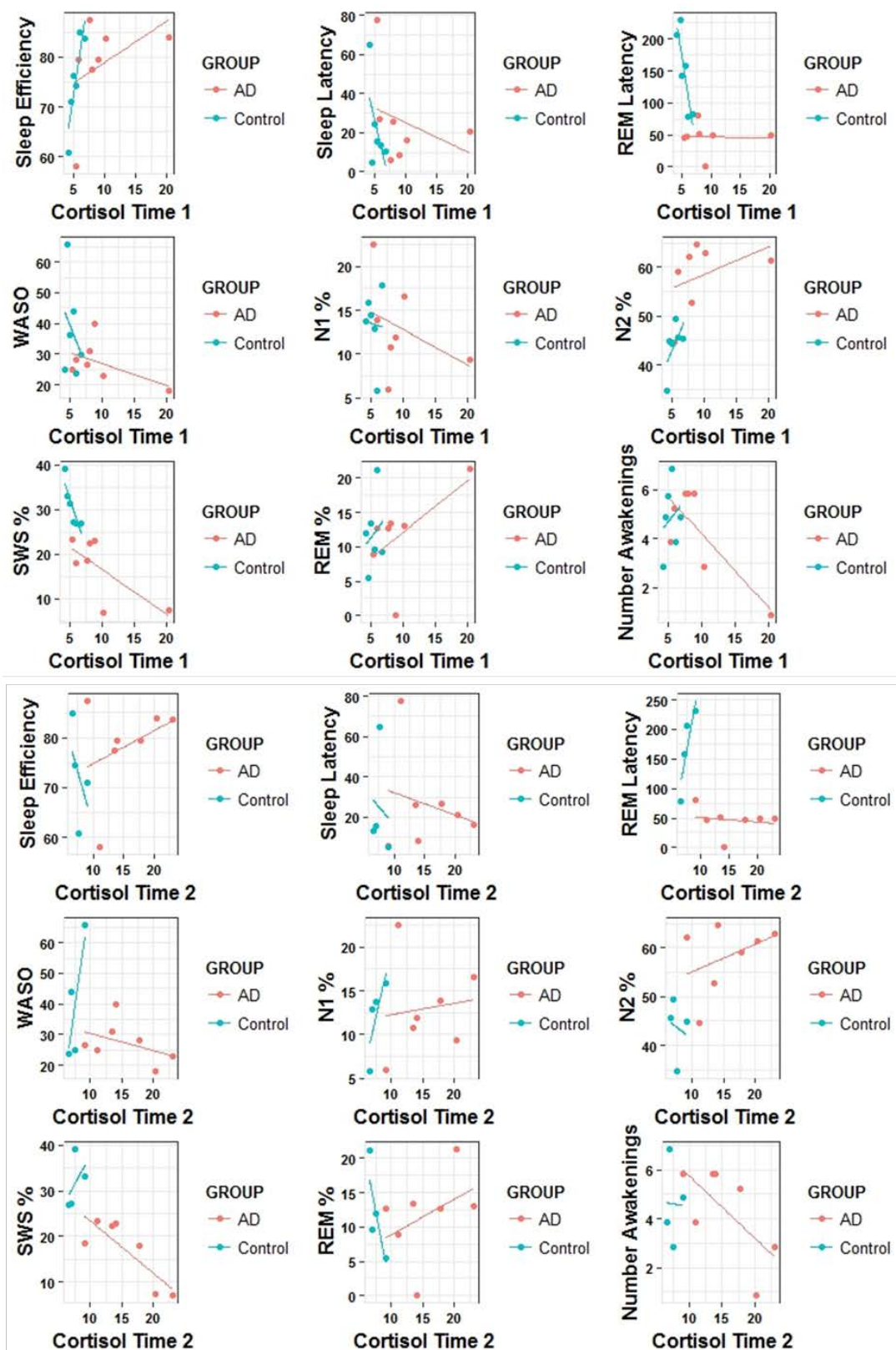
Mailing address: _____

Appendix J

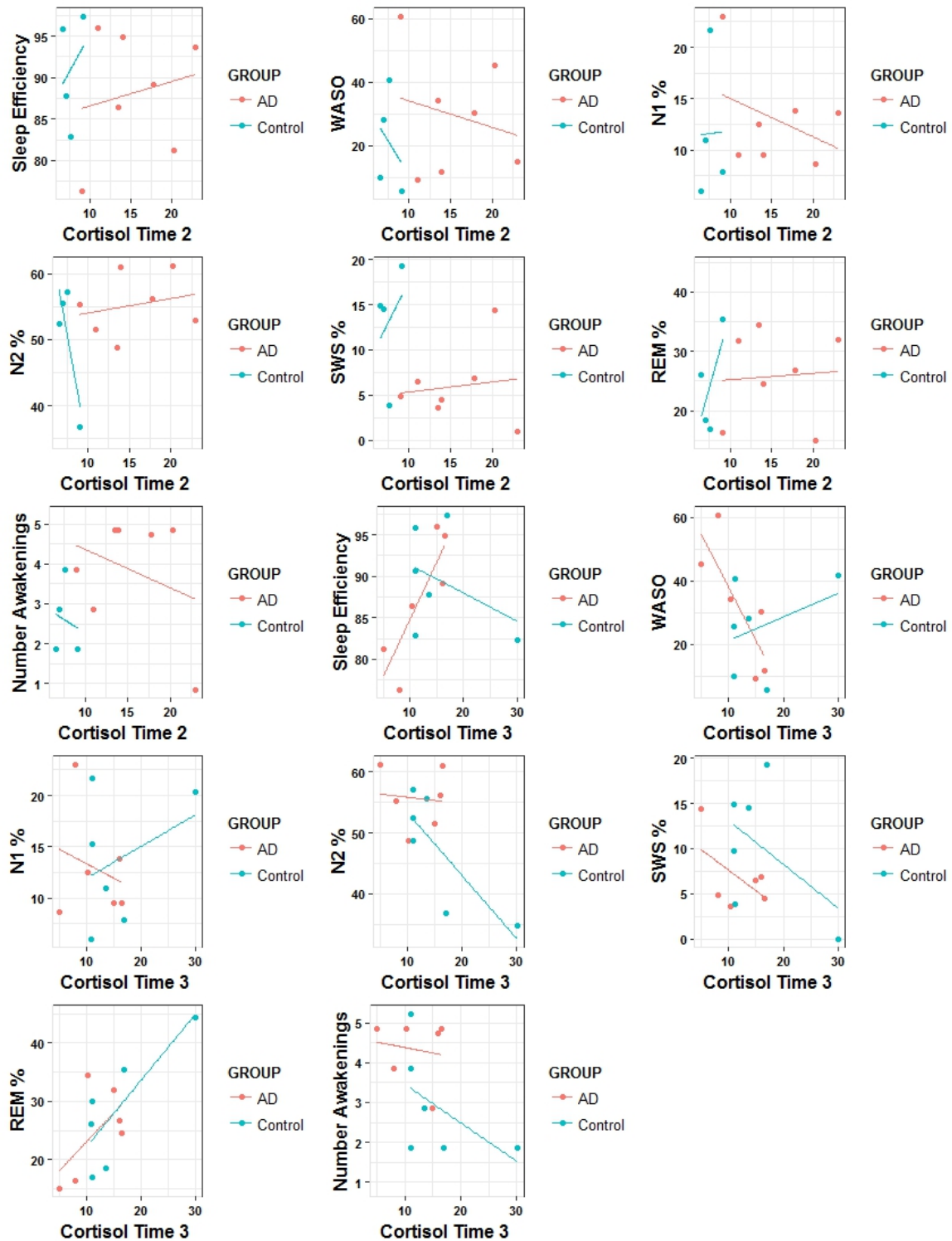
Supplementary Figures



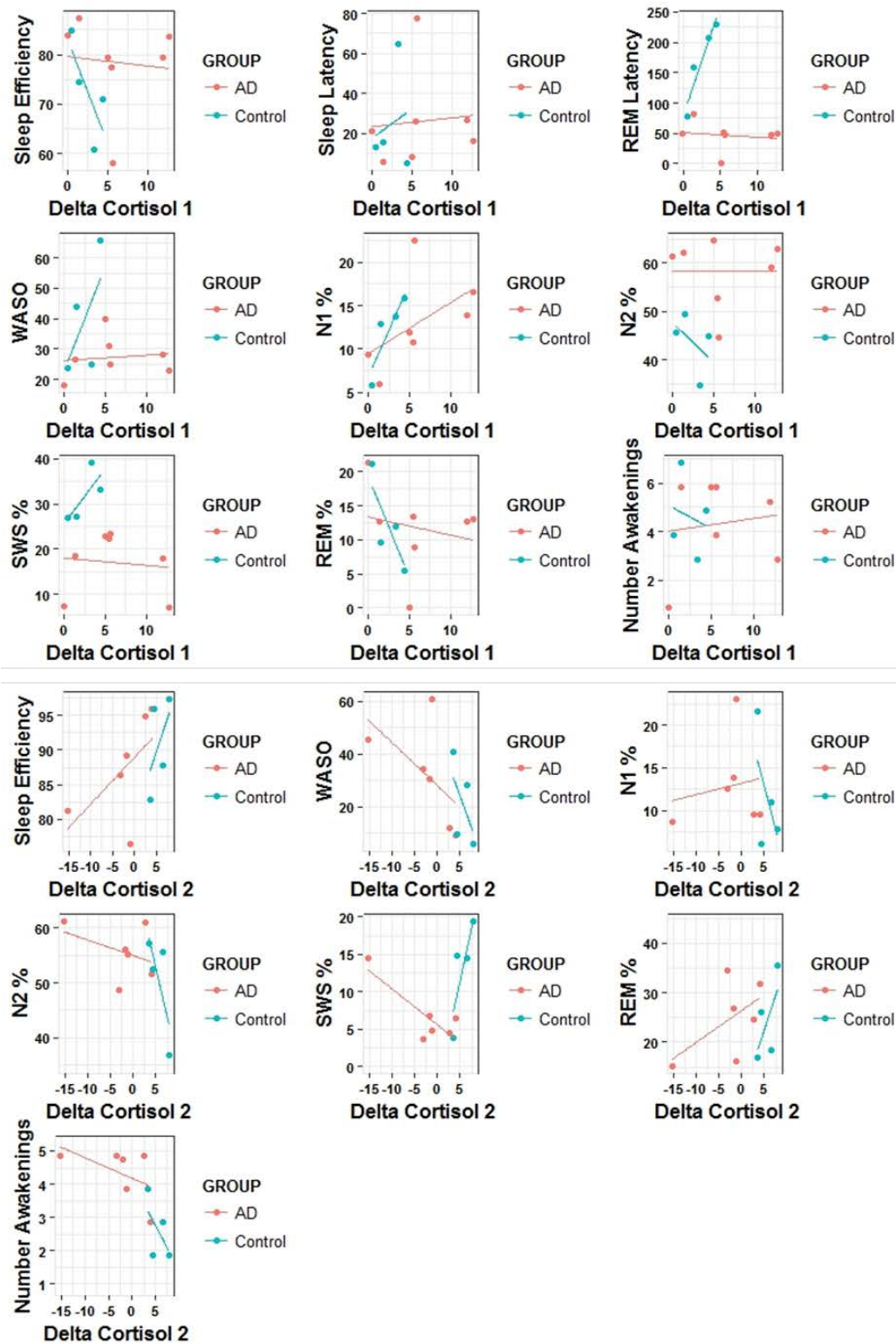
Supplementary Figure 1. Boxplots of sleep and cortisol outcome variables by group (Control vs AD) and disease characteristics (AD only). Extreme outliers are indicated by open circles and stars.



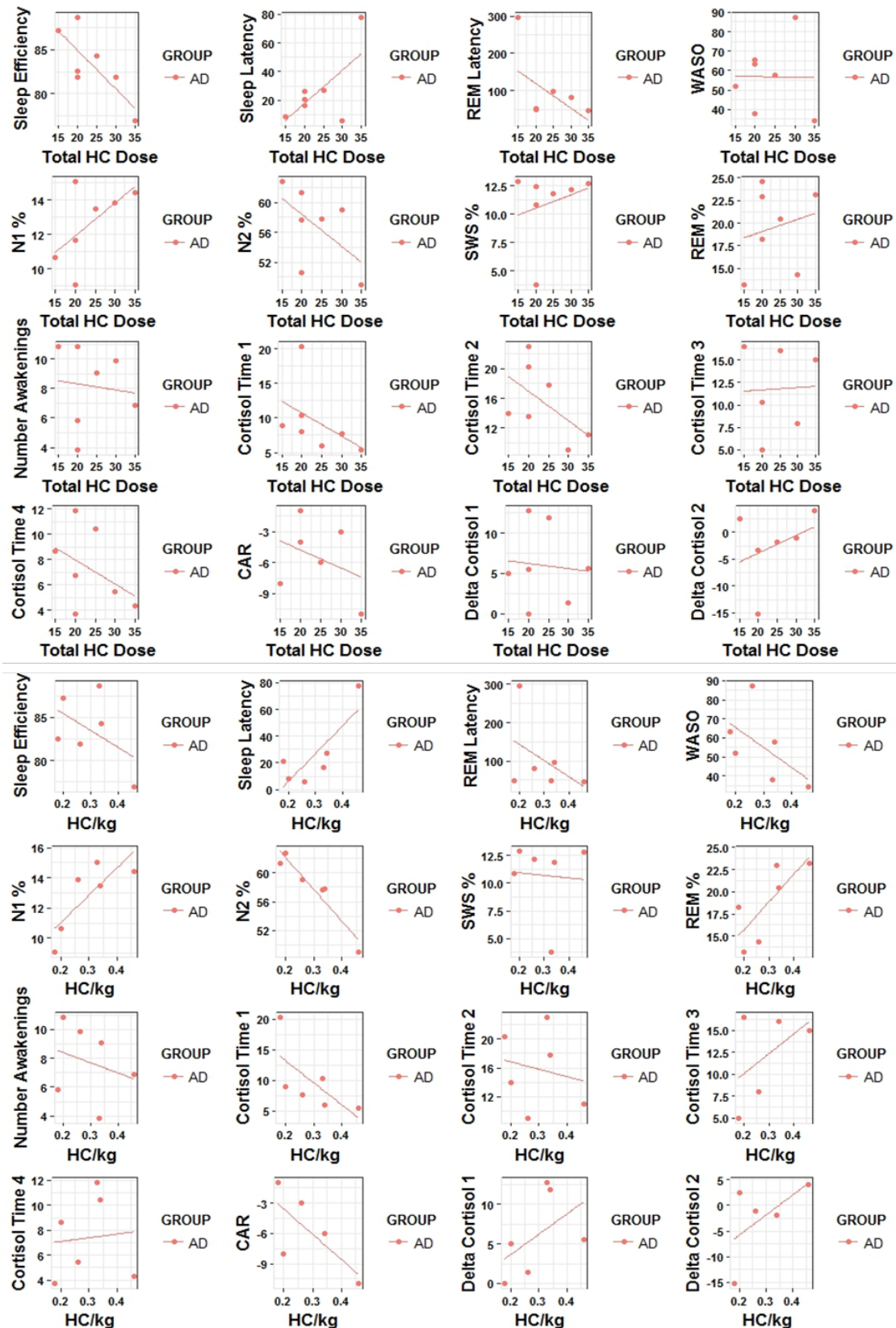
Supplementary Figure 2. Scatterplots depicting the relationship between cortisol at Time 1 (bedtime; 21h30) and Time 2 (midnight; 00h00) with sleep outcome variables across the first half of the night in patients with AD and Controls.



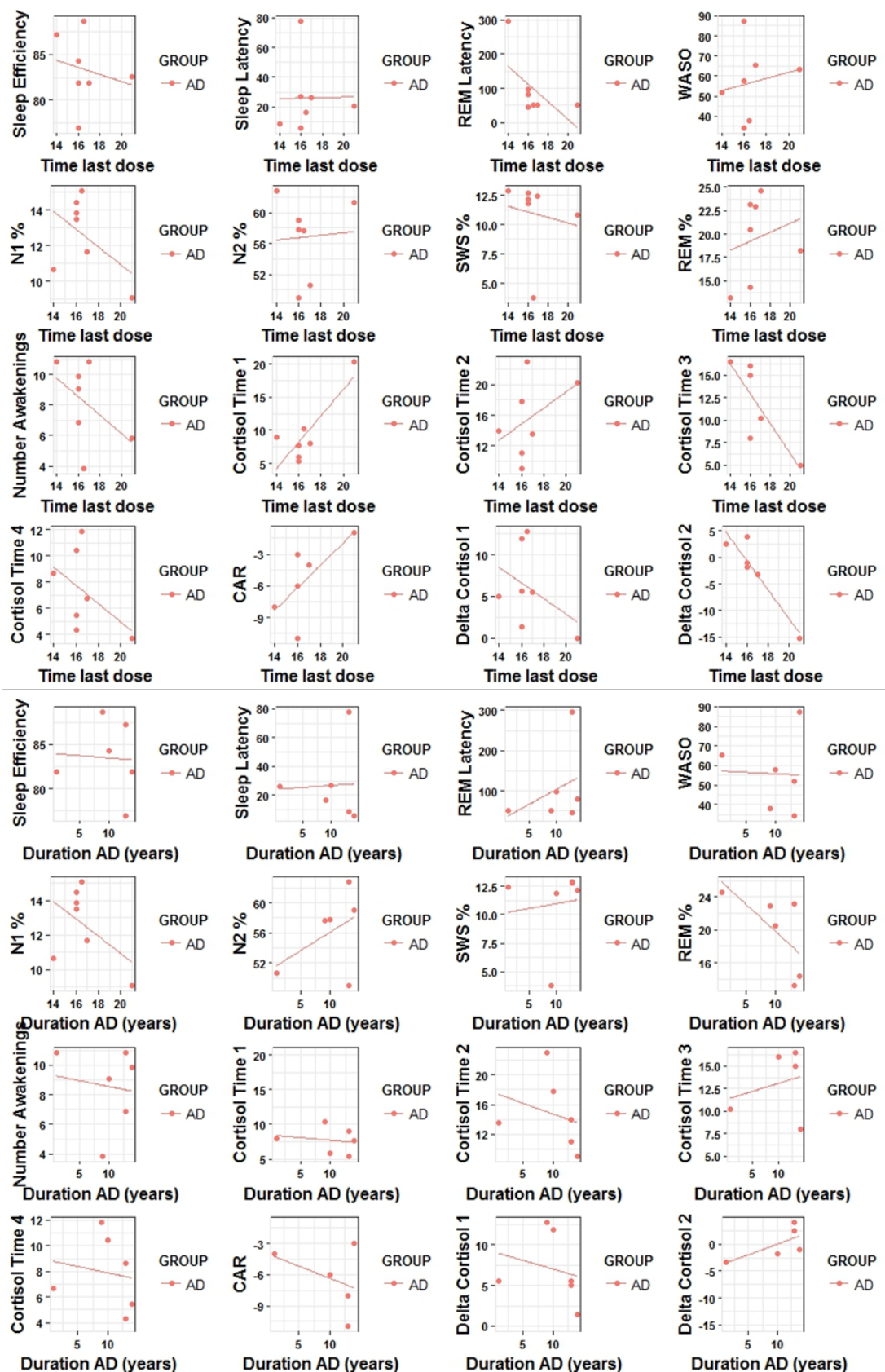
Supplementary Figure 3. Scatterplots depicting the relationship between cortisol at Time 2 (midnight; 00h00) and Time 3 (wake time; 06h00) with sleep outcome variables across the second half of the night in patients with AD and Controls.



Supplementary Figure 4. Scatterplots depicting the relationship between cortisol change in cortisol concentrations during the first (Delta Cortisol 1) and second (Delta Cortisol 2) half of the night and sleep outcome variables across the respective halves of the night in patients with AD and Controls.



Supplementary Figure 5. Scatterplots depicting the relationship between total hydrocortisone dose and dose per kilogram (HC/kg) with sleep and cortisol outcome variables across the whole night.



Supplementary Figure 6. Scatterplots depicting the relationship between time of last hydrocortisone dose and duration of AD with sleep and cortisol outcome variables across the whole night.

